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Novel functional imaging methods in depression and anxiety

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Abstract

Major depression and anxiety disorders are debilitating and prevalent conditions, yet current methods for tailoring treatments and predicting treatment response are suboptimal, in part due to a lack of understanding of the biological and behavioural bases of these disorders. Neuroimaging has provided some insights, but this area lacks a well-defined battery of trans-diagnostic psychological measures, and most neuroimaging studies have focused on pharmacological, rather than psychological therapies.

This thesis firstly details meta-analyses of the changes in brain activation and neural predictors of treatment response with psychological therapies to determine whether robust correlates exist currently. Further chapters aimed to pilot novel fMRI and behavioural methods in patients with anxiety and depression. Firstly, a human translation of a rodent task to measure fear and anxiety, which had yet to be piloted in patients with affective disorders, despite the relevance of threat-avoidance to these conditions. Secondly, a novel task to measure self-reflection more directly than currently available methods. Thirdly, a new and underutilised method of analysing resting-state data to reveal temporal variability in connectivity.

We were able to demonstrate consistent changes in brain activation associated with psychological therapies across depression and anxiety, though the meta-analyses highlight how far we are from utilising neuroimaging in clinical practice. We did not find significant differences in brain activation on the novel tasks between patients and controls; however, the task relating to self-reflection showed promise as a behavioural measure. We found increased fluctuations in connectivity between default mode network regions considered crucial for the generation of self-reflective thoughts in patients versus

controls. We were able to replicate this finding in an independent sample, suggesting the finding is robust.

These results contribute to an understanding of threat sensitivity and self-reflection in affective disorders and provide ideas for future research in to neural biomarkers and behavioural measures for these conditions.

Abbreviations

AAL	Automated anatomical labelling
ABM	Attentional bias modification
ACT	Acceptance and commitment therapy
ACQ	Agoraphobia Conditions Questionnaire
AES-SDM	Anisotropic effect size seed-based *d* mapping
AFNI	Analysis of Functional Neuroimages
ANOVA	Analysis of variance
BA	Brodmann area
BAS	Behavioural activation system
BATD	Behavioural activation therapy for depression
BDI	Beck Depression Inventory
BIS	Behavioural inhibition system
BMI	Body mass index
BOLD	Blood oxygen level dependent
CAPS	Clinician administered PTSD scale for DSM
CBT	Cognitive behavioural therapy
CSF	Cerebrospinal fluid
df	Degrees of freedom
dlPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Version IV
DVARS	Derivative of root mean square VARiance over voxelS
EEG	Electroencephalogram
EMDR	Eye movement desensitization and reprocessing therapy
EPI	Echo planar image
EPQ-R	Eysenck's Personality Questionnaire - Revised
F	Female
FDG	Fluorine-18-labelled deoxyglucose
FDR	False Discovery Rate

FIQT	Fake IQ test
(f)MRI	(functional) magnetic resonance imaging
FOV	Field of view
FSCSR	Forms of Self-Criticising/Attacking and Self-Reassuring scale
FSL	the FMRIB software library
FSS	Fear Schedule Survey
FWE	Family-wise error
FWHM	Full-width half maximum
GAD	Generalised Anxiety Disorder
(g)SAD	(generalised) social anxiety disorder
HARS	Hamilton Anxiety Rating Scale
HC	Healthy control
HDRS	Hamilton Depression Rating Scale
IAPT	Improving Access to Psychological Therapies Service
ICA	Independent component analysis
ICD-10	International Classification of Diseases – Version 10
ITI	Inter trial interval
IQ	Intelligence quotient
JORT	Joystick Operated Runway Task
LSAS	Liebowitz Social Anxiety Scale
M	Male
MÅDRS	Montgomery-Åsberg Depression Rating Scale
MBSR	Mindfulness Based Stress Reduction
MDD	Major Depressive Disorder
MDTB	Mouse Defence Test Battery
(m)PFC	(medial) prefrontal cortex
MINI 5.0	Mini International Neuropsychiatric Interview, Version 5.0
MNI	Montreal Neurological Institute and Hospital coordinate system
MP-RAGE	Magnetisation Prepared Rapid Acquisition GRE 3D Inversion Recovery
mPFC	Medial prefrontal cortex
NHS	National Health Service

NICE	National Institute for Health and Care Excellence
OCD	Obsessive compulsive disorder
PAG	Periaqueductal gray
PAS	Panic and Agoraphobia Scale
PCA	Principal component analysis
PCC	Posterior cingulate cortex
PD	Panic Disorder
PDSS	Panic Disorder Severity Scale
PET	Positron emission tomography
PSWQ	Penn State Worry Questionnaire
PTSD	Post-traumatic stress disorder
R&D	Research and Development
RMS	Root mean square
ROI	Region of interest
RRS	Ruminative Response Scale
SC	Self-criticism
SD	Standard deviation
SPECT	Single photon emission computed tomography
SPM	Statistical Parametric Mapping
SPQ	Spider Phobia Questionnaire
SSRI	Selective serotonin reuptake inhibitors
STAI	State Trait Anxiety Inventory
TE	Echo time
TR	Repetition time
Tc-99-ECD	Technetium-99m-ethyl cysteinate dimer
VAS	Visual analogue scale
WHO	World Health Organisation
WLS	Weighted least squares
YBOCS	Yale-Brown Obsessive Compulsive Scale
99mTc-HMPAO	99mtechnetium hexamethyl-propylene-amine-oxime

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I would like to acknowledge the people who have provided support and guidance at all stages of this work towards my PhD. I would especially like to thank my supervisors, Professor Anthony Cleare and Dr Adam Perkins, for their encouragement, guidance and invaluable advice. I have also been incredibly lucky to work with wonderful colleagues. I thank them all for their help and support: Caroline, Sue, Fiona, Dimos, Tim, Anjali, Nilay, Andres, Viryanaga, Viktoria, Nefize, Sinead, Dil, Val, Ema, Toby and Rachael. In particular, I'd like to thank Toby Wise who is a neuroimaging genius and has taught me so much, Rachael Taylor for her encouragement and assisting me with my job as I wrote up my thesis alongside working with her, and Becci Strawbridge who has imparted so much academic wisdom. I thank my mum, dad, Polly, Rebecka and Chris who have supported me along the way. Most of all I am grateful to all of the participants who consented to take part in these studies and made this research possible.

Overview and statement of the candidate's contribution to the work presented in this thesis

This thesis has been written having regard to the King's College London university guidelines that allow published work to be included and a modified thesis structure to be used. The thesis is therefore written with a general introduction and aims (Chapter 1), a meta-analysis (Chapter 2) and description of the main methods used (Chapter 3). There then follows three experimental chapters in which the three components of the thesis are described, with specific methods, results and a discussion of the results presented for each aspect of the study. These correspond to already published work where indicated, or planned publications. Finally, a full discussion bringing together all aspects of the work is presented in Chapter 7.

An outline of each chapter is given below along with a statement of contribution:

Chapter 1

This chapter provides a background to the thesis. I wrote all parts of this section, with guidance from Professor Anthony Cleare and Dr Adam Perkins.

Chapter 2

I independently conducted literature searches and performed statistical analyses for these meta-analyses of the neural correlates of psychological therapy. The chapter was written by me with assistance from Dr Toby Wise, Professor Anthony Cleare and Dr Adam Perkins.

Chapter 3

This chapter details the methodology of the fMRI (Study 1) and behavioural experiments (Study 2) in this thesis. I applied for ethics and funding for these projects, and solely recruited and conducted all participant visits (consulting Professor Anthony Cleare for clinical advice as required and receiving training on administering the clinical assessments). I also adapted a behavioural task, originally designed by Dr Adam Perkins for measuring self-reflection (the "Fake IQ test"), so as to be suitable as an fMRI paradigm, with the help of a programmer and advice of experts in the field of neuroimaging (Dr Owen O'Daly, Dr Roland Zahn, David Gasston and Alexandru Popescu). I wrote all parts of this chapter, with guidance from Professor Anthony Cleare and Dr Adam Perkins. A paper has been published about the utility of various recruitment methods used in this and other fMRI studies of patients with major depression (Wise et al., 2016).

Chapter 4

This chapter reports results from the Fake IQ test, a novel measure of self-reflection created by Dr Adam Perkins. I adapted this task to be suitable as an fMRI paradigm, with the help of a programmer (Alexandru Popescu) and advice of experts in the field of neuroimaging (Dr Owen O'Daly, Dr Roland Zahn and David Gasston). All data was collected independently by me and analysis conducted with advice from Dr Toby Wise due to his expertise with the analysis methodology. I wrote all parts of this chapter, with guidance from Professor Anthony Cleare and Dr Adam Perkins.

Chapter 5

This chapter analysed resting-state data using a recently developed analysis technique looking at dynamic functional connectivity in participants recruited in this thesis project

(Study 1) and in an independent sample of patients with major depression. Data for this additional sample was collected by Dr Toby Wise, Dr Danilo Arnone, Dr Andres Herane-Vives and me. The analysis scripts were created and analysis conducted by Dr Toby Wise. I contributed towards the pre-processing of fMRI data and behavioural analyses and jointly in the writing and theoretical analysis of the results. This work has been published in Translational Psychiatry where I am joint first author (Wise et al., 2017). The figures presented in this chapter are edited versions of the images in the published manuscript. The manuscript was reviewed by all named authors on the published paper, as well as anonymous reviewers.

Chapter 6

This chapter presents results on the Joystick Operational Runway Task, a measure of threat avoidance behaviour in patients from Study 1 and Study 2. I collected all data reported in this chapter. Scripts for fMRI data analysis were primarily written by Dr Toby Wise with whom I conducted data pre-processing and analysis and problem solved issues with the analysis script. The chapter was written by myself with guidance from Dr Adam Perkins, Dr Toby Wise and Professor Cleare. Figures 6-a and 6-b were kindly provided by Dr Perkins. The task was programmed by Robert Davis with technical support from David Gasston.

Chapter 7

This chapter provides an overall discussion of the work discussed in this thesis. It was written by myself with guidance from Professor Anthony Cleare and Dr Adam Perkins.

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Chapter 1: Introduction

1.1 General introduction and rationale

Major depression and anxiety disorders are highly prevalent and greatly impact a person's quality of life, affecting a wide range of functioning such as mood, physical health, social and cognitive ability (Olatunji et al., 2007; Wells et al., 1989; Wittchen et al., 2011). Comorbidity is common between the two conditions (Kaufman & Charney, 2000) and both respond to similar treatments (Ressler & Mayberg, 2007). Although there are many effective therapies for these disorders, a large proportion, around 40-60%, of patients do not respond to first-line recommended treatments which include evidence-based psychological therapies and antidepressant or anxiolytic medications (Baldwin et al., 2014; Cleare et al., 2015). Poor response rates and residual symptoms remaining post-treatment have significant individual and societal costs such as continued distress and increased probability of relapse, suicide risk, loss of productivity and wasted resources of inefficient treatment (Dunlop et al., 2011; Kennedy & Foy, 2005; Kessler et al., 2006).

Currently, psychiatric assessments are principally based on patient self-report and observation of patient behaviours without parallel measurement of the underlying biological mechanisms. Decisions regarding treatment are therefore based on clinical characteristics such as symptom severity, subtype, comorbidity and previous psychiatric history (Fava et al., 1997; Thase et al., 1997; Trivedi et al., 2006). These assessments are aided by the Diagnostic and Statistical Manual (American Psychiatric Association, 2013) and International Classification of Disease (World Health Organization, 1993) diagnostic systems.

However, patients vary widely in the pattern of symptoms they display suggesting there are multiple underlying causes and disease processes. A lack of understanding of the biological mechanisms underlying these heterogeneous disorders hampers the development of improved treatments or personalised medicine. Recent evidence from neuroscientific research has shown that existing clinical diagnostic categories, as outlined in the DSM and ICD, may lack accurate prediction of treatment response (Insel et al., 2010). This is potentially due to a failure to capture important pathophysiological mechanisms of these heterogeneous diseases in existing classification systems. Indeed, neuroimaging studies have shown evidence of new neurophysiological-based subtypes of disorders being better able to predict treatment response and symptoms (Clementz et al., 2015; Drysdale et al., 2017). A major goal in psychiatry is therefore the development of pathophysiological systems of diagnosis and predictors of response with the hope that they will lead to a more personalised treatment approach and better response rates by reducing the current trial-and-error approach to identifying the right treatment for patients (Insel et al., 2010).

One promising method of approaching this objective of a more biological approach in psychiatry is through identifying quantitatively measurable and specific dysfunctions in psychological or behavioural processes that are related to distinct brain structures and/or functions (Hyman, 2007). In recent years there has been a rapidly growing body of evidence to show that brain activation and morphology differs in emotional and cognitive domains in patients with depression and anxiety compared to healthy individuals (Etkin, 2010; Wise, Cleare, Vives, Young, & Arnone, 2014). There is also evidence to suggest that neural activation normalises over the course of therapy and that pre-treatment brain

activity can predict subsequent response to both pharmacological and psychological therapies (Fu et al., 2013; Ma, 2015; Messina et al., 2013; Shin et al., 2013).

Most functional imaging studies in affective disorders have studied response to emotional stimuli, for example, responses to both explicit and implicit presentations of emotional stimuli or the effect of emotional stimuli on ability to perform tasks of working memory or attention i.e. ability to gate out affective distractors (Etkin & Wager, 2007; Fonzo & Etkin, 2017; Treadway & Pizzagalli, 2014). Functional neuroimaging studies typically demonstrate an imbalance in neural activation in patients with anxiety and depression compared to healthy controls whereby abnormally elevated limbic activation is not adequately controlled by prefrontal regions (Etkin, 2010; Hariri et al., 2000; Rauch et al., 2000; Whalen et al., 2002). These findings align with a dual process model of emotion regulation with top-down prefrontal controlled processes and bottom-up, automatic limbic activation (Barrett et al., 2004). Prefrontal activation is involved in executive control (Owen et al., 2005) and emotional regulation processes (Ochsner & Gross, 2005), and has an inhibitory effect on limbic brain regions such as the amygdala, insula, hippocampus and anterior cingulate cortex (ACC), which are associated with intrinsic emotional reactivity (Drevets & Raichle, 1998; Phillips et al., 2003).

Patients with affective disorders who remit have been found to show recovery in the imbalance between these two systems (DeRubeis et al., 2008; Etkin et al., 2005; Siegle et al., 2007). DeRubeis et al. proposed that psychological therapies act to regulate emotional control processes by increasing activation in prefrontal emotional regulation systems which in turn have a top-down effect on limbic activation for depression (DeRubeis et al., 2008). An equivalent model in anxiety disorders has been proposed (Etkin et al., 2005).

Evidence for and against the dual-process model will be discussed in more depth in Chapter 2.

This field lacks a well-defined battery of performance-based, clinical measures which could aid the linking of psychiatric and neuroscientific findings (Insel et al., 2010). The development of robust neuropsychological measures of affective functioning – linking key personality dimensions of mental health to their underlying neural circuitry – could be a key step in achieving a more evidence-based approach to psychiatric treatment. It is important to understand the causes of response and non-response in patients to better target treatments and to also aid the development of improved or novel treatments. This is critical due to poor response rates in these conditions and many of the present pharmacological treatments for affective disorders, almost all of which target the monoaminergic system, being discovered by chance without a clear knowledge of the exact biological mechanisms of these disorders and treatment response.

Threat avoidance (an innate defensive reaction to fear and anxiety provoking situations) and self-reflection (inner consideration on personal thoughts, feelings and actions) are two such measurable neuropsychological domains of functioning relevant to both depression and anxiety disorders and for which there can be performance-based and well-defined tasks alongside validated measures of self-report. Both can be considered as dimensional constructs spanning several psychopathologies, which is encouraged in this line of biomarker research due to symptom overlap and communalities between structural and functional abnormalities between conditions (Cuthbert & Insel, 2013; Goodkind et al., 2015; McTeague et al., 2017). These psychological constructs are also associated with the activity of specific neural systems. Self-reflection is linked to the default mode network (DMN), two key areas being the medial prefrontal cortex (mPFC) and posterior cingulate

cortex (PCC) (Philippi & Koenigs, 2014). Threat avoidance is associated with midbrain regions such as the periaqueductal gray (PAG) and the hippocampus (Bach et al., 2014; Mobbs et al., 2009, 2007), along with amygdala-striatal and prefrontal cortex interactions (Collins et al., 2014; Delgado et al., 2009).

This thesis will pilot the ability of novel tasks, for measuring threat avoidance and self-reflection, to discriminate between patients and controls. The neural activity relating to these paradigms will be investigated in patients with depression and varying degrees of clinical anxiety versus healthy controls using functional magnetic resonance imaging (fMRI). The tasks will also be analysed in relation to behavioural performance in patients versus controls and in relation to response to cognitive behavioural therapy (CBT) (looking at changes pre- to post-therapy in responders versus non-responders to CBT) in order to validate these measures.

The task designed to measure self-reflection is a more implicit measure than typically used in this field of research (the potential advantages of which are outlined in Chapter 4). The task involves participants reflecting on their performance on a visual perception task which unknown to participants has no right or wrong answers and therefore individual differences in self-perception of performance are the measurements of interest. This fits with Beck's cognitive model of depression which was later also applied to anxiety (Beck, 1967; Beck et al., 2005). The theory states that depression and anxiety involve a distortion in perception and recall of environmental feedback in a negative direction: an inherent negative bias of the self, the world and the future.

The task utilised for measuring threat avoidance has previously been piloted in healthy individuals and task performance has been shown to be sensitive to anxiolytic medication

and related to personality traits associated with depression and anxiety, hence exploration here in patients with anxiety and depression. It is an active threat avoidance task and fits with Gray and McNaughton's Reinforcement Sensitivity Theory which postulates that patients with, and at risk of developing, anxiety have an overactive Behavioural Inhibition System (BIS, which is a system thought to regulate responses to aversive stimuli and goal-conflicts) and therefore demonstrate over-active avoidance of, and reactions in relation to, threats and punishment (Gray & McNaughton, 2000). Although the theory was originally developed in relation to anxiety, an overactive BIS is also a common finding in depression (Bijttebier et al., 2009).

1.2 Meta-analysis of the neural effects of psychological therapy

This thesis will begin on meta-analyses synthesising our current level of knowledge on the neural correlates of psychological therapies and neural predictors of psychological treatment response in depression and anxiety disorders. Psychological therapies are considered effective first-line treatments for these disorders according to national guidelines and are often a preferred form of treatment for many patients (Baldwin et al., 2014; Cleare et al., 2015). Despite this, there have been far fewer neuroimaging studies in relation to psychological therapies compared to pharmacological treatments (Etkin, et al., 2005). A recent meta-analysis has been published looking at pharmacological neuroimaging research in depression (Ma, 2015) but an update is required for psychological therapies, conducted with improved methodology (Messina et al., 2013).

Gaining a greater understanding of the mechanisms of psychological therapies is important in order to understand processes which underlie their clinical effectiveness and

for achieving the goal of precision psychiatry, by determining on an individual level who will respond best to which specific pharmacological or psychological therapy. This links to the work throughout this thesis as, if we are to incorporate neuropsychological assessments into clinical practice, we need to consider the evidence to date regarding neural associations of therapy to understand how close we are to understanding the neurobiological mechanisms of treatments and also in developing personalised predictors of response from this research field.

Additionally, the psychological and behavioural domains under investigation in this thesis (self-criticism and threat avoidance) may be more closely related to psychological than pharmacological therapies. For example, self-criticism has been found to be predictive of treatment response to psychological but not pharmacological therapies (Rector et al., 2000) and the therapies which target maladaptive threat avoidance are typically psychological in nature.

1.3 Self-reflection in depression and anxiety disorders

Self-reflection is a broad domain and includes both positive and negative aspects. For example, self-reflection of one's behaviour can help us perceive social cues, generate social emotions and also contributes to emotional regulation and self-insight (Philippi & Koenigs, 2014). Maladaptive levels of, and/or excessively negative, self-reflection, for example, excessive rumination, worry, and self-critical thoughts can be found in mood and anxiety disorders (Ingram et al., 1987; Woodruff-Borden et al., 2001) and pathological levels of these thoughts are key features of these conditions (American Psychiatric Association, 2013; Clark & Wells, 1995; Nolen-Hoeksema, 2000; 2008).

Neuroimaging research has begun to reveal the brain regions associated with self-reflection. The mPFC is considered crucial for the generation of self-reflective thoughts from various fields of evidence including neurological patients, and functional and structural neuroimaging studies. In patients with mPFC lesions, impaired self-reflection, for example diminished empathy, shame, guilt and social disinhibition, is found (Barrash, et al., 2000; Beer et al., 2003; Eslinger & Damasio, 1985; Philippi et al., 2012). Additionally, patients with neurodegenerative diseases associated with degeneration of the mPFC, for example, patients with frontotemporal dementia, show psychopathic traits such as loss of empathy and disinhibition, which may be mediated by the reduced self-reflection found in this patient group (Rascovsky et al., 2011). Functional neuroimaging studies, in both patient and healthy control groups, also support the relevance of the mPFC in self-reflection. The DMN which consists of the mPFC, PCC, and lateral parietal brain regions, has been found to be more active at rest (during unconstrained thought) than at the time of completing directive tasks (Buckner et al., 2008; Greicius et al., 2003; Raichle et al., 2001). When participants undergo a resting-state scan, where they are given no instructions other than to rest, they often report being engaged in self-reflective thought, for example, thinking about themselves, their future goals, and memories. The level of engagement in self-reflective thoughts has been found to be positively associated with DMN activity suggesting this network, which includes the mPFC, is involved in the generation of these thoughts (Andreasen et al., 1995; D'Argembeau et al., 2005; Mason et al., 2007; McKiernan et al., 2006).

Additionally, the mPFC and PCC (key regions within the DMN) are frequently found to be activated in tasks of self-referential processing, for example, personality judgement tasks where the participant has to judge how relevant certain personality traits are to

them or others (D'Argembeau et al., 2005; Moran et al., 2006; Whitfield-Gabrieli et al., 2011). Furthermore, Moran et al. (2006) and D'Argembeau et al. (2005) were able to demonstrate that the level of activation in the mPFC and PCC was positively correlated with the amount of self-reflection reported in these personality trait judgements.

In depression and anxiety disorders, heightened DMN activity has been found in both resting-state and task based neuroimaging (Berman et al., 2011; Drevets et al., 2008; Greicius et al., 2007; Mayberg, 1997; Zhu et al., 2012). There is evidence that this heightened DMN activity is correlated with rumination and symptom severity in both depression and anxiety disorders (Berman et al., 2011; Drevets et al., 2008; Greicius et al., 2007; Mayberg, 1997; Zhu et al., 2012). Therapy has also been found to normalise aberrant connectivity and activation levels within regions of the DMN. This has been found with CBT (Yoshimura et al., 2014), antidepressants (Li et al., 2013; Posner et al., 2013) and transcranial magnetic stimulation (Liston et al., 2014).

Given the importance of self-reflection in emotional regulation and self-awareness, processes which are crucial for psychotherapy to be effective (Mansell, 2011), it makes sense that high levels of self-criticism are associated with poorer treatment response. Indeed, self-criticism has been found to be associated with lower response rates to interpersonal therapy (Marshall et al., 2008) and CBT (Rector et al., 2000). Also, the degree to which self-criticism reduces during treatment has been found to be a significant predictor of treatment outcomes for depression (Rector et al., 2000) and social phobia (Rector et al., 2000). Self-criticism has also been linked to increased risk of co-morbidity and negative psychosocial outcomes in mental health conditions (Dunkley et al., 2003; Kopala-Sibley et al., 2015).

The work in this thesis aimed to test self-reflection in two original ways:

1. A novel implicit self-reflection measure called The Fake IQ test (see Chapter 4) where participants' satisfaction with their performance on an impossible visual perception task was assessed. This task was designed with consideration to avoid some of the issues with existing measures of self-reflection. The task measures self-perception of performance including self-satisfaction and self-other comparison. The relationship between task measures and self-report self-criticism, rumination and worry scores will be explored.
2. Dynamic functional connectivity, an underutilised method of analysing resting-state data, in areas crucial for the generation of self-reflective thought: the mPFC and PCC of the DMN (see Chapter 5). The novelty of the resting-state analysis comes from looking at temporal (dynamic) variability in connectivity, a relatively new technique, which goes beyond studying averaged (or static) connectivity in neural networks, which is an analysis technique that has been applied widely in affective disorders.

1.4 Threat avoidance in mood and anxiety disorders

Threat avoidance is an innate defensive reaction to potential threats and is an evolved survival behaviour that all animals exhibit (Mobbs, et al., 2015). The inability to extinguish or inhibit high levels of threat response is common to all anxiety disorders (Graham & Milad, 2011; Otte, 2011). Threat avoidance and escape are coping strategies that are widely used by patients with anxiety whereby a patient learns to minimise or prevent contact with events or stimuli that they have learnt to be aversive (LeDoux et al., 2017), for example, avoidance of social situations in those with social phobia (Barlow,

2013), repellent stimuli in people with contamination fears (Tsao & McKay, 2004), and in depression generally withdrawing and/or complaining (Ferster, 1973). These avoidant behaviours can be very successful at temporarily reducing symptoms of fear and anxiety, and are thus strongly reinforced via operant conditioning processes which leads to the continuation of these behaviours (Mowrer, 1951). However, problems arise when these avoidance behaviours lose their adaptive qualities by preventing people from learning which situations are and are not dangerous, become habitual or excessive, and interfere with daily life and social functioning; and are thus seen as maladaptive forms and levels of threat avoidance (LeDoux et al., 2017).

Maladaptive threat avoidance is not specific only to anxiety and has also been associated with obsessive-compulsive disorder (OCD), major depressive disorder (MDD), suicidality and autism (Gillan et al., 2014; Servatius, 2016). Understanding differences between adaptive versus maladaptive forms of threat avoidance in individuals is important and the construct has been proposed to be dimensional, spanning several pathologies to differential degrees, rather than a specific symptom identifying a diagnosis (Gillan et al., 2014; Servatius, 2016). Threat sensitivity may therefore help explain psychiatrically-relevant individual differences in proneness to affective disorders, specific symptoms and their severity, and response to treatments. Additionally, understanding the neurological differences underlying maladaptive and adaptive threat avoidance may help target and develop more effective behavioural or pharmacological treatments.

Currently the understanding of the need to challenge maladaptive avoidance underpins many treatments for these disorders, for example flooding or exposure therapy for specific or social phobias (Mineka, 1979), or emotional processing therapy which encourages individuals to fully process, and not avoid, disturbing events and thought processes (Foa

& Kozak, 1986). These therapies are therefore based on the principles of classical and operant conditioning (how the disorders are proposed to be learnt and maintained respectively in Mowrer's two-factor theory of avoidance learning (Mowrer, 1951)). The therapies work by exposing the individual to perceived threats until habituation - a reduction in behavioural and sensory threat responses due to repeated exposure - has occurred. An additional element to these therapies is response prevention which involves encouraging the individual to refrain from avoidance and escape behaviours, which in turn reduces the reinforcement of these behaviours. Therefore, these treatments act to extinguish maladaptive coping strategies and work on the understanding that the conditions can be learned and unlearned using similar principles. Additionally, medications can help reduce fear and anxiety either as adjuncts to cognitive and/or behavioural therapies or independently by addressing underlying neurochemical causes.

Despite the significant impact that the understanding of threat avoidance has had on the development of psychological therapies, there is a paucity of neurobiological research into active threat avoidance in human pathology with much of the initial research having been conducted pre-clinically in animals (LeDoux et al., 2017). However, the animal models generally align with what has been found in humans to date. During active avoidance fMRI tasks, concurring brain regions involved during threat-avoidance include the amygdala, hippocampus, nucleus accumbens, PAG and mPFC (Bach et al., 2014; LeDoux et al., 2017; Mobbs et al., 2009).

An important element to consider when researching pathological human threat avoidance is the type of avoidance involved in the task. A model has been developed in which active threat avoidance behaviours (i.e. threats requiring action for their avoidance) can be differentiated in terms of their defensive direction. Fear is associated with orientation

away from pursuing threats (where escape is possible, leading to flight behaviour), whereas anxiety is associated with more ambiguous threats which require investigation and therefore necessitate orientation *towards* the threat (for example, risk assessment and goal-conflict behaviours when escape is not possible) (Gray & McNaughton, 2000).

Evidence for this differentiation in terms of defensive direction comes from rodent studies which show that drugs with clinical effectiveness against affective disorders differentially alter defensive behaviour (Blanchard et al., 1990). Drugs for panic disorder have been found to specifically lessen fear-related threat behaviours i.e. reactions to threats where escape is possible (Griebel et al., 1995), whereas drugs that treat generalised anxiety disorder (GAD) moderate rodent behaviour during goal-conflict tasks where escape is not possible i.e. the rodents run from their predators less fast or not at all which is an illustration of altered risk assessment behaviours to ambiguous threats (Blanchard et al., 1990). This suggests that affective disorders reflect alterations in the functioning of brain systems that govern responses to threat and that individuals with anxiety disorders exhibit not only elevated threat avoidance but also that there are distinctions between disorders (Blanchard et al., 2001). This distinction is supported anecdotally by the tendency of patients with panic disorders to feel the urge to escape or avoid situations in which a panic attack is likely to occur (American Psychiatric Association, 2013). Whereas patients with GAD tend to experience anxiety in more complex situations where escape is not always possible, which leads to worrying about many aspects of life (American Psychiatric Association, 2013).

Chapter 6 of this thesis will explore threat avoidance behaviour in patients with MDD and varying degrees of clinical anxiety versus healthy controls behaviourally and via fMRI using a task developed by Dr Adam Perkins which allows the measurement of both fear

and anxiety simultaneously within subjects. These two types of defensive direction had previously been studied in isolation of one another in humans until the development of this task - the Joystick Operated Runway Task (JORT) (Perkins et al., 2011; 2009). The JORT has been piloted in healthy controls but has yet to be tested in a patient population which is important as the task cleverly taps into both fear and anxiety concurrently and there may be important distinctions within and between disorders which could improve our understanding of specific threat avoidance behaviours and their associated neural activity in disorders.

1.5 General aims and objectives

The research reviewed here indicates that there are clear functional neuroimaging differences between patients with depression and anxiety disorders versus healthy individuals. These results have not yet been translated into clinical practice by improving treatments or tailoring therapies at an individual level according to likely response. The thesis begins with meta-analyses to determine consistencies regarding the neural correlates of psychological therapies and neural predictors of psychological treatment response in depression and anxiety disorders to determine whether robust markers exist in the current literature.

There is a lack of research into threat-avoidance or direct measures of self-reflection in this field which, for the reasons outlined above, could be important psychological measures for aiding the linking of psychiatric and neuroscientific findings. The aim of the studies presented in this thesis was to assess the utility of novel fMRI paradigms and a new analysis technique of resting-state data in discriminating patients with depression

and anxiety versus healthy controls. Additionally, neural activation on the tasks will be explored in relation to self-report measures to validate the tasks as measuring relevant concepts. The three fMRI paradigms tested on patients versus healthy controls were: 1) The Fake-IQ test – a novel MRI paradigm to study brain activity relating to self-reflection; 2) Multi-echo resting-state fMRI – assessing dynamic functional connectivity in the DMN and the association of instability in this network with self-report self-reflection measures; and 3) The JORT - investigating neural activity to threat – the first time to be reported in a patient population (Perkins et al., 2013).

The tasks relating to threat-avoidance and self-reflection are novel in this field of research and therefore this work will also assess these tasks behaviourally to determine if significant differences in behavioural outcomes or task-related self-report measures in patients versus controls are found. Additionally, we sought to determine whether task performance was associated with subsequent response to treatment, or if treatment was associated with changes in performance on these tasks. This aim hopes to determine the validity of the tasks for use in neuroimaging studies of therapeutic response. Additionally, we aimed to test whether the 'Fake' nature of the Fake IQ test was perceived by participants and if participants placed importance on performing well at the task.

Chapter 2: Meta-analyses of the neural effects and predictors of response to psychological therapy in depression and anxiety

Chapter Summary

A better understanding of the neural mechanisms underlying the effects of psychological therapy in depression and anxiety disorders could aid understanding of the recovery process and help target more effective treatments; however, research to date has yielded inconsistent findings. The dual process model hypothesises that psychological therapy should be associated with increased emotional-regulation and cognitive control processes in prefrontal brain regions and consequently to this decreased implicit emotional reactivity in limbic regions.

Meta-analyses of 1) brain activity changes accompanying psychological therapy (22 studies, n = 352) and 2) neural predictors of symptomatic improvement (11 studies, n = 293) in depression and anxiety disorders were conducted on eligible studies using seed-based *d* mapping. To ensure only the most robust findings were reported, a jackknife sensitivity analysis was conducted and publication bias assessed via tests of funnel plot asymmetry.

The most robust findings were of significant decreases in activation in clusters in the anterior cingulate/paracingulate gyrus, left and right inferior frontal gyrus and insula after therapy relative to pre-therapy. There was only one significant cluster of activation

that was predictive of subsequent symptom change which met our inclusion for robustness, located in the right cuneus.

These meta-analyses suggest that there are consistent functional brain changes that occur after psychological therapy in depression and anxiety disorders. The results are in agreement with neural models of improved self- and emotional-regulation following psychological therapy as evidenced by decreased activity within the anterior cingulate and insula. We propose compensatory as well as corrective neural mechanisms of action underlie therapeutic efficacy and suggest the dual process model may be too simplistic to account fully for the neural mechanisms of treatment. More research on predictors of psychotherapeutic response is required to provide reliable and potentially clinically useful predictors of psychological treatment response across disorders.

2.1 Introduction

Psychological interventions are first-line treatments for both depression and anxiety disorders (Baldwin et al., 2014; Cleare et al., 2015; NICE, 2009), but are ineffective for as many as 50% of patients (Cuijpers et al., 2014; Loerinc et al., 2015). Research investigating the neural correlates of therapy aims to provide a greater understanding about the formation and maintenance of symptoms, in addition to the development of improved treatments and personalised medicine according to likely response (Lueken & Hahn, 2016), which could improve outcomes for recipients of psychological interventions. Recent reviews have shown the promise of functional neuroimaging studies in this field

for both depression and anxiety disorders (Fu et al., 2013; Hamilton et al., 2012; Ma, 2015; Wise et al., 2014). A meta-analysis was recently published for pharmacological neuroimaging studies in depression (Ma, 2015) but an update is required for psychological therapies, conducted using improved methodology (Messina et al., 2013).

Neuroimaging studies take either a longitudinal approach, where patients are scanned before and after therapy, or a predictive approach where patients are scanned before therapy to determine pre-treatment brain activation predictors of subsequent symptomatic improvement. Longitudinal studies aim to identify changes in regional brain activity that is associated with the therapeutic mechanisms of the intervention. In contrast, prediction studies aim to provide a basis for stratified treatment according to likely response, potentially enabling clinicians to more effectively tailor therapies at an early stage to individual patients (Fu et al., 2013). These complementary approaches may serve as a tool for clinical decision-making, along with behavioural markers gained from them.

As described in the introductory chapter (Chapter 1), the dual process model is the leading theory regarding how psychological therapies are proposed to regulate emotional processing in both depression and anxiety disorders: by increasing activation in prefrontal, emotional regulation systems which in turn have a top-down effect on elevated limbic activation (Etkin et al., 2005). A recent systematic review of functional neuroimaging studies in depression and anxiety concluded that the results offer support for the dual process model of psychological therapies. However, there are inconsistencies in the literature regarding the specific brain regions and direction of activation changes within regions (Goldapple et al., 2004; Linden, 2008) with some research being at odds with the model; for example, certain studies have found decreased pre-frontal activation

following psychological therapy (Taylor & Liberzon, 2007). Theoretically, this is not entirely unexpected as hyper-prefrontal activation has been associated with ruminative thinking which would be expected to reduce with therapy (Goldapple et al., 2004). Additionally, in post-traumatic stress disorder (PTSD) decreases in prefrontal activation have been associated with a reduction in the intrusiveness of traumatic memories (Lindauer et al., 2008).

For several reasons, findings from neuroimaging studies of treatment response may not be robust when considered independently: studies often have small sample sizes, which make it difficult to find strong effects of therapy after applying multiple comparisons across the whole brain (Button et al., 2013). Meta-analyses in the field of neuroimaging provide an effective way to determine consistencies across datasets with improved statistical power.

2.1.1 Aims and hypotheses

The aim of this study was to use meta-analyses to determine the most robust findings with psychological therapy in two domains: 1) functional brain activation changes from before to after psychological therapy, and 2) pre-treatment brain activation predictors of subsequent symptomatic improvement in patients with depression and/or anxiety disorders. To our knowledge this is the first prediction meta-analysis published in this field across depression and anxiety. Both disorders were included in analyses due to high levels of comorbidity between the two (Brown et al., 2001; Kaufman & Charney, 2000), indeed anxiety has been identified as a risk factor for developing depression (Wittchen, et al., 2007) and some cases of depression lead to anxiety, with stress being a predisposing factor for both disorders (Nutt, 2004). Additionally, there are overlapping symptoms,

similarities in their neurochemistry (for example, imbalances have been found in similar neurotransmitter systems such as serotonin function), and both disorders respond to similar therapies such as selective serotonin reuptake inhibitors (SSRIs) and CBT (Ressler & Mayberg, 2007). However, there are distinctions between the two disorders, for example, differential responses have been found to certain pharmacological treatments such as benzodiazepines which are effective for anxiety disorders but not depression or OCD and SSRIs are typically effective at higher doses for panic disorder and OCD than depression (Nutt, 2004). Also, although there is a genetic overlap, there are also genetic differences between disorders (Otowa et al., 2016; Smith et al., 2016; Smoller, 2016). In this meta-analysis, both disorders are included despite these caveats as the same theory is used to model therapeutic response in these disorders (Messina et al., 2013). Further, meta-analyses across psychiatric disorders have found evidence of more similarities in functional and structural neuroimaging abnormalities across disorders than differences, despite variance in symptoms (Goodkind et al., 2015; McTeague et al., 2017). Additionally, all psychological interventions were considered due to evidence of commonalities between therapies, the so called dodo effect (Luborsky et al., 2002; Rosenzweig, 1936).

We applied a thorough and conservative approach to identify only the most robust findings within this heterogeneous literature. In line with the main theory used to model longitudinal results in this field, the dual process model, we hypothesised that psychological therapy would be associated with increased prefrontal activity and reduced limbic activity post- compared to pre-therapy. We hypothesised that increased baseline ACC activation would be predictive of greater symptomatic improvement in accordance with results from a meta-analysis by Fu et al., (2013) in depression studies and a recent

review by Lueken & Hahn (2016) of neuroimaging predictors of response in anxiety and depression.

2.2 Methods

2.2.1 Literature searches and study selection

Literature searches were conducted in the following electronic databases: Scopus (Elsevier, http://www.scopus.com) and Medline (Ovid Technologies Inc., http://ovidsp.uk.ovid.com), to identify articles published before 24.07.2017. The searches identified studies using MRI, single photon emission computed tomography (SPECT) or positron emission tomography (PET) (see Appendix 1 for full list of search criteria). The title and abstract of all retrieved articles were evaluated to check suitability. Reference lists of included articles and relevant reviews were also manually searched.

The following eligibility criteria were applied:

- Articles were excluded if they did not include subjects currently meeting DSM or ICD established diagnostic criteria for MDD; bipolar disorder; dysthymia; OCD; PTSD; panic disorder; social anxiety disorder; GAD; or specific phobia.
- Studies looking at the above affective disorders alongside neurological conditions were excluded to ensure findings were not obscured by neurological pathology.
- Participants were required to have been scanned prior to beginning a course of psychological therapy and have examined pre-treatment regional brain activation in relation to post-treatment change in symptom severity (prediction studies) or brain activity changes pre- to post-therapy (longitudinal studies).

- Articles were excluded if they were case reports, reviews, meta-analyses or not written in English.
- Only adult samples were suitable; child, adolescent or geriatric populations were excluded to minimise the effect of neurodevelopmental and neurodegeneration confounders on brain activation. In geriatric populations, there is an increased likelihood that organic disorders underlie, contribute to, or confound depressive symptoms. Older patients are therefore likely to show age-specific neuroimaging correlates of psychological therapy (e.g. Aizenstein et al., 2014; Smith et al., 2009). In adolescents, neurodevelopmental features need to be taken into account and inconsistencies have been found between adolescent and adult findings (Kerestes et al., 2014).
- Articles that used a region of interest (ROI) approach only, did not apply consistent statistical thresholds throughout the brain, or did not report peak coordinates in stereotactic space were excluded. Selecting only whole brain results is important as publication bias is likely to be less problematic with these analyses due to a more exhaustive and unbiased inclusion of studies and brain regions compared to ROI analyses.
- Both task-based and resting-state functional scanning paradigms were included. In order to control for any methodological differences observed between these two types of studies, standard anisotropic effect-size seed-based *d* mapping (AES-SDM) meta-analyses were conducted separately for task-based and resting-state studies and a meta-regression was conducted controlling for paradigm type to increase methodological homogeneity, where the number of studies permitted. This approach was taken as it is known that functional paradigm type can affect

results and regions of activation (Fu et al., 2007; Messina et al., 2013; Palmer et al., 2015; Whitfield-Gabrieli et al., 2011).

- To ensure no overlap between studies, in the case of multiple studies reporting the same patient group (for example, reporting results of different functional tasks), we included the largest sample or, in studies following up the same participant group at a range of time points post-therapy, the study reporting scanning at the time-point closest to therapy completion.

2.2.2 Meta-analyses

Analyses were carried out using AES-SDM (Version 5.141, released December 2016, (Radua et al., 2014). AES-SDM is a voxel-based, weighted meta-analytical method which creates voxel-level maps based on effect size and variance of peak coordinates reported within studies and analyses them with random-effects meta-analytic methods. T-statistics are converted to effect sizes using standard statistical techniques. Effect size is calculated exactly at the reported peak coordinates and estimated, depending on distance from the peak, for the surrounding voxels using an anisotropic un-normalized Gaussian kernel multiplied by the effect size of the peak, subject to tissue-type constraints. This is similar to the method used in an alternative neuroimaging meta-analytic technique called activation likelihood estimation (ALE, http://brainmap.org/ale); however, AES-SDM is able to provide a more accurate estimation of signal due to accounting for effect size in calculations (Radua et al., 2012). AES-SDM also has the advantage of permitting the analysis of heterogeneity between studies via meta-regressions. It addresses between-study heterogeneity by counteracting the effects of studies reporting opposite activation

findings in the same region by reconstructing both positive and negative maps in the same image, unlike other methods (Radua et al., 2012).

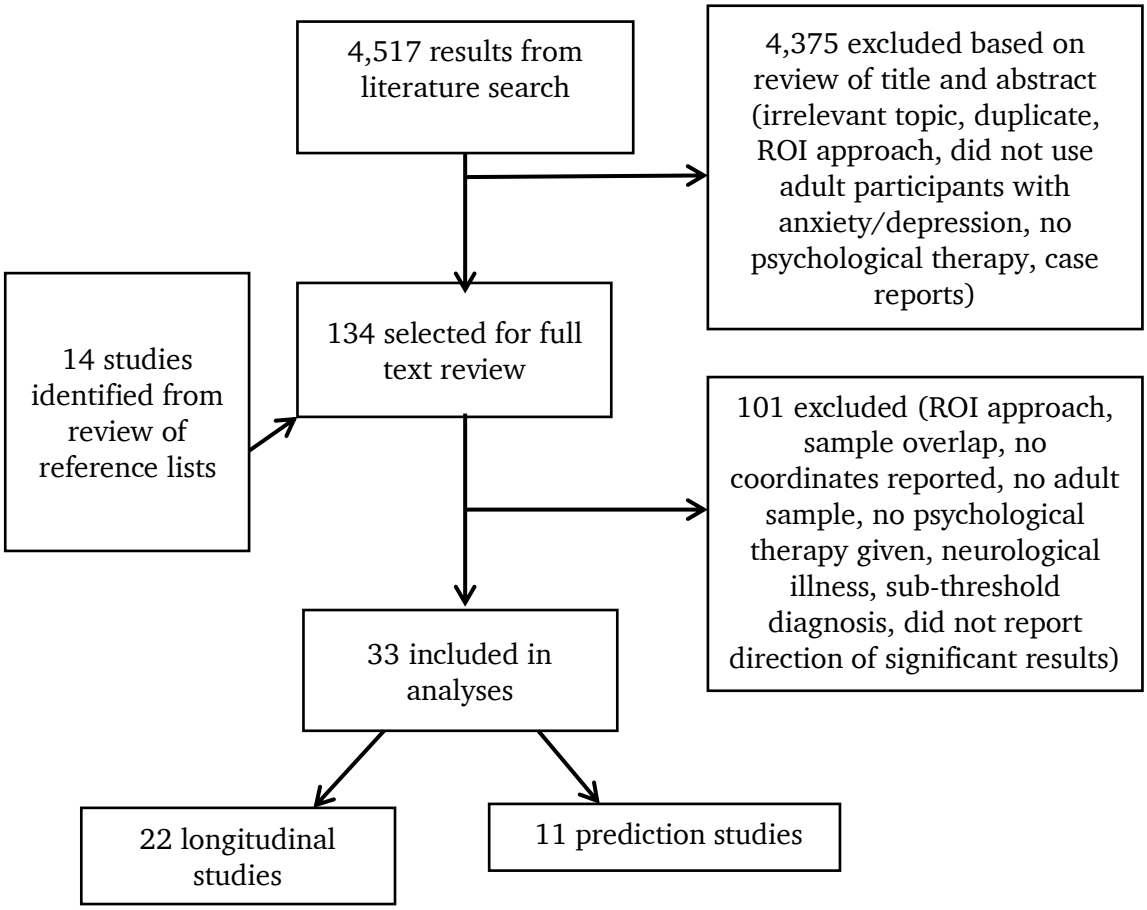
As suggested by (Radua & Mataix-Cols, 2012), voxels with a p-value <.005 were considered as significant, but those from clusters with fewer than 10 voxels or peaks with AES-SDM Z-values <1 were discarded to reduce the false positive rate. To determine the most robust results and explore the influence of outliers, a jackknife sensitivity analysis was conducted to assess the contribution of individual studies to the overall results. This repeats the analyses removing one study per iteration. If brain regions remain significant in all or most of the combinations then it can be concluded that these findings are highly replicable. Results were excluded that did not remain significant in 10% or more of iterations. To assess publication bias, funnel plots of effect size estimates of peak voxels were visually inspected and an Egger regression test was implemented to examine funnel plot asymmetry (Egger et al., 1997). This was conducted using the metafor package for R software (Viechtbauer et al., 2010) (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/). The potential effect of paradigm type (task versus resting state scans) was examined by simple linear models and by repeating standard AES-SDM meta-analyses in subgroups.

2.3 Results

2.3.1 Literature searches

Scopus returned 3,559 and Medline 958 results. From these, 33 articles were suitable for inclusion in analyses (see Figure 2-a for search details).

Figure 2-a: Flowchart of process of publication selection.



Abbreviations – ROI; Region of interest.

2.3.2 Longitudinal results

Twenty-two whole brain longitudinal studies (n = 352 patients) met eligibility criteria and were included in these analyses (see Table 2-a for study details). The studies comprised the following patient groups: panic disorder (n = 5); PTSD (n = 4); social anxiety disorder (n = 5); unipolar major depression (n = 3); specific phobia (n = 2); OCD (n = 2); and GAD (n = 1). Disorder severity was typically in the moderate to severe range.

Table 2-b and Figure 2-b provide details of all significant clusters from the longitudinal studies (n=22), regardless of whether they met our criteria for reliability and robustness. Details of jacknife sensitivity analysis, visual inspection of funnel plots, and publication bias analyses are detailed in the table (see Appendix 2 for funnel plots, however it should be noted that with relatively few, small studies funnel plots are insensitive to publication bias, so this cannot be excluded). All regions survived our sensitivity analysis and Eggers regression (all *ps* >.05), though some regions showed signs of publication bias in visual inspection of funnel plots. The most robust results, with no evidence of publication bias, were that psychological therapy was associated with significantly decreased activity post- compared to pre-therapy, in the left anterior cingulate/paracingulate gyri, the right inferior frontal gyrus and left inferior frontal gyrus/insula.

There were too few studies that met our eligibility criteria to perform meta-regressions to study heterogeneity between disorders or therapy type (Radua et al., 2010). Standard AES-SDM analyses were repeated and limited to task (n= 17) and resting-state studies (n= 5). The separate analyses showed that the clusters found overall (see Table 2-b) in the corpus callosum and left ACC/paracingulate gyri remained consistent across both subgroups (see Tables 2-c and -d). The right inferior network, right arcuate network, bilateral inferior frontal gyri and right middle frontal gyrus findings were only found in resting-state studies. Left inferior frontal gyrus and left insula (which was an additional, separate cluster for task-based studies) and left temporal pole / mid temporal gyrus were significant findings in task-based analysis only. This was confirmed with a linear model confirming significant differences in task versus resting state studies in these regions.

Table 2-a: Characteristics of longitudinal studies included in the meta-analyses

Study	Disorder	N (female)	Type of therapy	Imaging technique	Task	Severity	Medication	Comorbidities	Age (years)
Aupperle et al. (2013)	PTSD	14 (14)	Cognitive Trauma Therapy (mean 11.57 +-1.6 sessions)	fMRI	Emotional processing (anticipation and presentation of negative vs. positive images)	11 met full and 3 partial DSM-IV criteria, average pre-treatment CAPS score 66.07+-16.78	None	Excluded bipolar disorder or schizophrenia	40.07 +-7.44
Baioui et al. (2013)	OCD	12 (8)	CBT (31 sessions)	fMRI	Symptom provocation (individualised OCD trigger photos)	Met DSM-IV criteria for OCD, pre-treatment YBOCS score 23.08+-12.63, illness duration at least 4 months	16.67%	4 patients had comorbid axis I disorders (2 SP; 2 MDD; 1 SAD)	32.49 +-8.89
Beutel et al. (2010)	PD	9 (6)	Psychodynamic therapy (4 week intensive inpatient programme)	fMRI	Emotion regulation (emotional go/no-go task)	Met ICD-10 criteria for PD, 2 with agoraphobia, pre-treatment average score on agoraphobic cognitions questionnaire 2.04+-0.67	44.44%	Not stated	32
Felmingham et al. (2007)	PTSD	8 (5)	Imaginal exposure therapy and cognitive restructuring (8 sessions)	fMRI	Emotional face processing (fearful vs. neutral)	Met DSM-IV criteria for PTSD following assault (n=4) or car accidents (n=4)	25%	4 patients had comorbid MDD. Excluded psychosis and BPD	36.8 +-8.8
Furmark et al. (2002)	SAD	6 (-)	Group CBT (8 sessions)	FDG PET	Symptom provocation (public speaking task)	Met DSM-IV criteria for social phobia (3 generalised)	None	None, excluded all other current psychiatric disorders	-
Goldapple et al. (2004)	MDD	14 (-)	CBT (15-20 sessions)	FDG PET	Resting state	Met DSM-IV criteria for MDD, mean pre-treatment HDRS score 20+-3	None	Patients with other axis 1 disorders were excluded	-
Goldin & Gross (2010)	SAD	14 (8)	MBSR (8 sessions)	fMRI	Emotional reaction to negative self-beliefs	Met DSM-IV criteria for SAD	None	Excluded all Axis 1 disorders except SAD, GAD, agoraphobia, or specific phobia	-
Goldin et al. (2012)	SAD	24 (-)	MBSR (8 sessions)	fMRI	Self-referential encoding task (negative>self)	Met DSM-IV criteria for SAD (primary diagnosis)	None	Exclusion criteria included thought disorders, bipolar depression, and alcohol or drug dependence.	-

Goossens et al. (2007)	SP (spider)	16 (16)	Group exposure CBT (1 session, 4-5 hours)	fMRI	Symptom provocation (phobia vs. neutral images)	Diagnosed using the MINI (DSM), mean score on SPQ pre-treatment - 23.05+-2.88	None	Free from other lifetime history of psychopathology other than spider phobia	24 +-3.02
Hölzel et al. (2013)	GAD	15 (9)	MBSR (8 weeks)	fMRI	Emotional face processing (angry versus neutral)	Met DSM-IV criteria for GAD.	20%	Comorbidities: N=4 MDD, n= 5 SAD.	38.5 +-13.3
Kircher et al. (2013)	PD	42 (29)	CBT (12 sessions)	fMRI	Fear conditioning	Met DSM-IV criteria for PD, PAS pre-treatment score 25.97, HAM-A 24.38	None	31 patients had 1 or more comorbidities. Excluded psychotic or bipolar I disorder, BPD.	35.42 (-)
Klumpp et al. (2013)	gSAD	14 (9)	CBT (12 sessions)	fMRI	Emotional face processing (fearful versus happy)	Met DSM-IV criteria for SAD. Moderate to severe severity: pre-treatment LSAS 71.21+-9.61	14.29%	Excluded current MDD, severe depressive symptoms, history of bipolar or psychotic disorder	28.07 +-8.62
Lindauer et al. (2008)	PTSD	10 (4)	Brief eclectic psychotherapy (16 sessions)	99mTc HMPAO SPECT	Symptom provocation (trauma scripts)	Met DSM-IV criteria for PTSD, pre-treatment PTSD score 11.7+-1.6	None	n=3 mild depression. Excluded: schizophrenia, psychotic disorders, bipolar disorder, moderate/severe depression, PD, phobia, OCD and dissociative disorders.	-
Månsson et al. (2013)	SAD	22 (-)	ABM (4 weeks, 8 sessions, n=11), iCBT (9 week course, n=11)	fMRI	Emotional face processing (disgust vs. neutral)	Met DSM-IV criteria for SAD, pre-treatment LSAS-SR: iCBT 76.00+-20.3; ABM 75.25+-19.2	36.36% ABM group, 45.45% iCBT group	Excluded current MDD	-
Pagani et al. (2007)	PTSD	15 (-)	EMDR (5 sessions)	99mTc HMPAO SPECT	Symptom provocation (recollection of the traumatic event)	Met DSM-IV criteria for PTSD	None	Not stated	-
Prasko et al, (2004)	PD	6 (3)	Group CBT (6 weeks, 18 sessions, plus 2 individual booster sessions)	FDG PET	Resting state	Met DSM-IV criteria for PD with or without agoraphobia, mean pre-treatment PDSS score 16.5+-5.05	None	Patients with other axis 1 disorders were excluded	31.8 (-)
Sakai et al. (2006)	PD	11 (9) all responders	CBT (10 sessions)	FDG PET	Resting state	Met DSM-III-R criteria, median pre-treatment PDSS score 16	None	Excluded: current MDD, bipolar, schizophrenia, social phobia, OCD, PTSD, GAD, personality disorder	29.26 +-6.39

Sankar et al. (2015)	MDD	16 (13)	CBT (16 sessions)	fMRI	Self-referential processing	Met DSM-IV criteria for MDD, average pre-treatment HDRS score 21.88+-1.89	None	Comorbid axis 1 disorders were excluded	40.00 +-9.27
Schienle, et al. (2007)	SP (spider)	14 (14)	Group CBT/exposure (one 4 hour session)	fMRI	Symptom provocation (phobia vs. neutral images)	SPQ pre-treatment score: 21.9+-1.7	None	Not stated	27.2 +-9.2
Seo et al. (2014)	PD	14 (10)	Group CBT (12 sessions)	Tc-99-ECD SPECT	Resting state	Met DSM-IV criteria for PD, average pre-treatment PAS score 24.86+-11.98	78.57%	Patients with other axis 1 disorders were excluded	32.3 +-9.02
Yamanishi et al. (2009)	OCD	33(19) responders only	Intensive behavioral therapy (12 weeks, sessions 1-5 times per week)	Tc-99-ECD SPECT	Resting state	Met DSM-IV criteria for OCD, average pre-treatment YBOCS score 33.5+-4.5	100%	Patients with other axis 1 disorders were excluded	34.7 +-7.1
Yoshimura et al. (2014)	MDD	23 (7)	Group CBT (12 sessions)	fMRI	Negative self-referential processing	Met DSM-IV criteria for MDD, average pre-treatment HDRS 11.0+-4.8	100%	Does not state (excluded psychotic disorder / bipolar)	37.3 +-7.2

Missing data coded (-): PTSD, post-traumatic stress disorder: OCD, obsessive compulsive disorder: (g)SAD, (generalized) social anxiety disorder: PD, panic disorder: MDD, major depressive disorder: SP, specific phobia: FDG PET, fluorine-18-labelled deoxyglucose positron emission tomography: SPECT, single photon emission computed tomography: 99mTc-HMPAO, 99mtechnetium hexamethyl-propylene-amine-oxime :Tc-99-ECD, technetium-99m-ethyl cysteinate dimer, fMRI, functional magnetic resonance imaging: DSM, Diagnostic and Statistical Manual of Mental Disorders: ICD, International Statistical Classification of Diseases and Related Health Problems: LSAS, Liebowitz Social Anxiety Scale: PAS, Panic and Agoraphobia Scale: PDSS, Panic Disorder Severity Scale: HDRS, Hamilton Depression Rating Scale: HAM-A, Hamilton Anxiety Rating Scale; YBOCS, Yale-Brown Obsessive Compulsive Scale: STAI, State-Trait Anxiety Inventory: SPQ, Spider Phobia Questionnaire; EMDR, eye movement desensitization and reprocessing therapy: ABM, attentional bias modification: (i)CBT, (internet-based) cognitive behavioural therapy: CAPS, Clinician-Administered PTSD Scale for DSM: MBSR, Mindfulness Based Stress Reduction.

Table 2-b: **Regions of significant difference in brain activation change pre-to post-treatment**

Regions	Peak MNI coordinate	SDM Z-value	*p*	Number voxels	BA
Neural activation: Post- > Pre-therapy					
Right inferior network, inferior longitudinal fasciculus[1]	30, -62, -4	1.05	0.0007	118	-
Right arcuate network, posterior segment[2]	40, -54, 22	1.02	0.0008	82	-
Corpus callosum[1]	28, -62, 10	1.02	0.0008	19	-
Neural activation: Post- < Pre-therapy					
Left anterior cingulate / paracingulate gyri*	-2, 44, 4	-1.98	<0.0001	1548	10
Left inferior frontal gyrus, opercular part, left insula[3]	-50, 10, 14	-1.91	<0.0001	775	44
Right inferior frontal gyrus, triangular part*	48, 32, 20	-1.92	<0.0001	761	45
Left middle frontal gyrus[4]	-30, 52, 6	-1.30	0.001	101	10
Right temporal pole, middle temporal gyrus[5]	46, 4, -34	-1.20	0.002	64	20
Right middle frontal gyrus, orbital part[4]	26, 48, -14	-1.17	0.003	37	11

MNI, Montreal Neurological Institute; SDM, seed-based d mapping; BA, Brodmann Area. ***Clusters surviving all tests of robustness and publication bias. [1] Driven only by two studies: Goldin & Gross (2010) and Yamanishi et al. (2009) and funnel plots showed evidence of publication bias in this cluster. [2] Driven only by Yamanishi et al. (2009)[3] Driven only by Kircher et al. (2013). [4] Driven only by two studies: Goldapple et al. (2004) and Yamanishi et al. (2009) and a funnel plot showed evidence of publication bias in this cluster. [5] Driven by Kircher et al., 2013 and Prasko et al. (2004) and a funnel plot showed signs of publication bias in this cluster.**

Table 2-c: Regions of significant difference in brain activation change pre-to post-treatment– task-based studies only

Regions	Peak MNI coordinate	SDM Z-value	*p*	Number voxels	BA
Neural activation: Post- > Pre-therapy					
Right and left precuneus / corpus callosum[1*]	6, -56, 38	1.19	0.0002	995	7/23
Neural activation: Post- < Pre-therapy					
Left inferior frontal gyrus, opercular part[2]	-50, 10, 14	-1.80	<0.0001	576	44
Left anterior cingulate / paracingulate gyri / right anterior cingulate [3*]	-8, 44, -2	-1.67	0.0001	504	10
Left insula[2]	-38, 0, -10	-1.21	0.003	66	48
Right temporal pole, middle temporal gyrus[4]	-46, 4, -34	-1.21	0.003	64	20

Abbreviations - MNI, Montreal Neurological Institute; SDM, seed-based d mapping; BA, Brodmann Area. **N = 274. *Clusters surviving all tests of robustness [1] Driven by (P. Goldin et al., 2012). [2] Driven by Kircher et al. (2013) and eggers regression test showed signs of publication bias. [3] Driven by Kircher et al. (2013). [4] Driven by two studies: Kircher et al. (2013); Klumpp et al. (2013).**

In task-based studies only, all but one region survived jackknife analysis criteria (the right temporal pole/middle temporal gyrus, see Table 2-c). The most robust findings were the precuneus increased activation and ACC deactivation post-therapy, which showed no signs of publication bias.

Table 2-d: Regions of significant difference in brain activation change pre-to post-treatment – resting-state studies only

Regions	Peak MNI coordinate	SDM Z-value	*p*	Number voxels	BA
Neural activation: Post- > Pre-therapy					
Right lingual gyrus / right inferior network, right fusiform gyrus[1]	22, -60, -8	1.62	0.0003	686	19
Right arcuate network, posterior segment[1]	40, -60, 20	1.61	0.0004	232	-
Corpus callosum[1]	26, -64, 14	1.50	0.001	23	-
Neural activation: Post- < Pre-therapy					
Right middle frontal gyrus, right inferior frontal gyrus *	48, 34, 18	-2.51	0.00005	949	45
Left middle frontal gyrus [1]	-34, 56, 10	-2.30	0.00007	565	10
Right middle frontal gyrus, orbital part[1]	30, 46, -18	-2.31	0.00006	279	11
Right anterior cingulate / paracingulate gyri / left anterior cingulate[1]	4, 50, 12	-2.13	0.0002	250	32

MNI, Montreal Neurological Institute; SDM, seed-based d mapping; BA, Brodmann Area. **N=78. *Cluster surviving all tests of robustness. [1] Driven by Yamanishi et al. (2009).**

In resting state studies only, none of the above clusters showed signs of publication bias in visual inspection of funnel plots and none had significant Egger regressions (see Table 2-d). Due to few studies meeting eligibility for this analysis (n = 5), the only cluster meeting our criteria for robustness, surviving all iterations of the jackknife sensitivity analysis, was the right middle frontal gyrus. All other clusters were driven by one study.

2.3.3 Prediction results

Eleven whole brain pre-treatment neuroimaging prediction studies (n = 293 patients) meeting eligibility criteria were included in this analysis (see Table 2-e for study descriptions). All studies had looked at pre-treatment neural activation in relation to change in scores on measures of symptom severity. The studies comprised the following patient groups: PTSD (n = 2); social anxiety disorder (n = 5); OCD (n = 2); MDD (n = 1) and panic disorder (n = 1).

Only one cluster survived jackknife sensitivity analysis (a cluster with peak coordinates in the right cuneus cortex which extended into the right superior occipital gyrus and right middle occipital gyrus); jackknife analysis revealed the other clusters were not robust. We report the results of all clusters in Table 2-f and Figure 2-b. Evidence of publication bias was observed in all clusters' funnel plots which was supported by an Egger regression test with trend significance for the cluster of decreased activation ($t(1, 10) = -2.17$, $p = 0.055$).

There were too few studies that met our eligibility criteria to perform meta-regressions (Radua et al., 2010) to study heterogeneity between disorders, therapies or methodologies (all but one study was task-based). When the meta-analysis was re-run on only studies which had used a task during scanning (n = 10), the four significant clusters as per the original analysis remained unchanged.

Table 2-e: Characteristics of prediction studies included in the meta-analyses

Study	Disorder	N (female)	Type of therapy	Imaging technique	Task	Severity	Medication	Comorbidities	Age (years)	Prediction measure
Aupperle et al. (2013)	PTSD	14 (14)	Cognitive Trauma Therapy (mean 11.6 +-1.6 sessions)	fMRI	Emotional processing (anticipation and presentation of negative versus positive images)	11 met full and 3 partial DSM-IV criteria, score>=30 on CAPS, average pre-treatment CAPS score 66.07+-16.78	None	Excluded bipolar disorder or schizophrenia	40.07+-7.44	Change in CAPS score
Burklund, et al. (2017)	SAD	36 (-)	CBT (n=17) or ACT (n=19) both 12 sessions	fMRI	Dynamic social threat task (rejecting versus neutral phrases)	Met DSM-IV criteria for primary/co-primary SAD and clinical severity rating of >4/8	Some (-%)	Excluded bipolar disorder, substance-related disorders, suicidality, or psychosis.	-	Change in LSAS score
Carl et al. (2016)	MDD	33 (22)	BATD (mean 11.7+-4.4 sessions)	fMRI	Monetary incentive delay task (anticipation of reward)	Met DSM-IV-TR criteria for MDD, pre-treatments HDRS score of ≥15	None	Excluded current suicidal ideation, anxiety and mood disorders other than unipolar depression or dysthymia, psychosis, substance disorders, past psychosis or bipolar disorder.	33.2 +-6.5	Change in BDI
Doehrmann et al. (2013)	gSAD	39 (14)	Group CBT (12 sessions)	fMRI	Emotional face processing (angry vs. neutral)	Met DSM-IV criteria for SAD, pre-treatment LSAS score of 81.8+-13.4	None	13 participants had comorbid anxiety disorders (6 GAD, 5 SP, 3 anxiety disorder NOS, PD 3, hypochondriasis 1)	29.3+-7.9	Change in LSAS score
Falconer, et al. (2013)	PTSD	13 (8)	CBT (8 sessions)	fMRI	Executive Inhibition (Go/No-Go task)	-	46.15%	Excluded history of psychosis or BPD. Comorbidities included: MDD (n=8); PD (n=1)	38.30+-12.16	Change in CAPS score
Klumpp et al. (2014)	gSAD	21 (15)	CBT (12 sessions)	fMRI	Emotional face processing (fearful/angry vs happy)	Met DSM-IV criteria for gSAD, moderate to severe severity: pre-treatment LSAS = 72.5+-11.6	9.52%	Excluded current MDD, severe depressive symptoms, history of bipolar or	24.9+-6.3	Change in LSAS score

								psychotic disorder, did not exclude comorbid anxiety disorders, SP (n=3), GAD (n=3), PD (n=1)		
Klumpp et al. (2016)	gSAD	32 (24)	CBT (12 sessions)	fMRI	Emotional conflict resolutions (fear vs. neutral)	Met DSM-IV criteria for gSAD as primary complaint. Baseline LSAS 74.3+-14.9	None	Comorbid disorders not excluded: 10 GAD, 2 PD, 2 MDD, 4 dysthymia, 3 SP, 1 PTSD, 1 adjustment disorder	25.4+-5.1	Change in LSAS score
Klumpp et al., (2017)	SAD	34 (22)	CBT (12 session)	fMRI	Emotion regulation task (reappraise versus looking at negative images)	Met DSM criteria for SAD (primary diagnosis), moderate to severe: pre-treatment LSAS 77.7 +-14.0	None	Comorbid disorders not excluded: 11 GAD, PD 4, SP 3, PTSD 1, adjustment disorder 1	25.0 +-4.7	Change in LSAS score
Olatunji et al. (2014)	OCD	12 (6)	CBT (24 sessions)	fMRI	Symptom provocation	Inpatients. Met DSM-IV criteria for OCD, mean pre-treatment YBOCS 32.25(+-5.73)	66.70%	Excluded psychosis but no other axis 1 disorders were excluded.	32.25 (range 18-53)	Change in YBOCS score
Reinecke et al. (2014)	PD	14 (10)	CBT (4 sessions)	fMRI	Emotion regulation	Met DSM-IV criteria for PD (8 with agoraphobia)	None	Comorbidities: 3 SP, 1 SAD. Excluded current or past psychotic or bipolar disorder.	37.2+-11.1	Change in ACQ score
Yamanishi et al. (2009)	OCD	45 (26)	Intensive behavioral therapy (12 weeks,)	**Tc-99-ECD** SPECT	Resting state	Met DSM-IV criteria for OCD, average pre-treatment YBOCS score 33.81 (combined group mean calculated)	100%	Patients with other axis 1 disorders were excluded	34.01 (-)	Change in YBOCS score

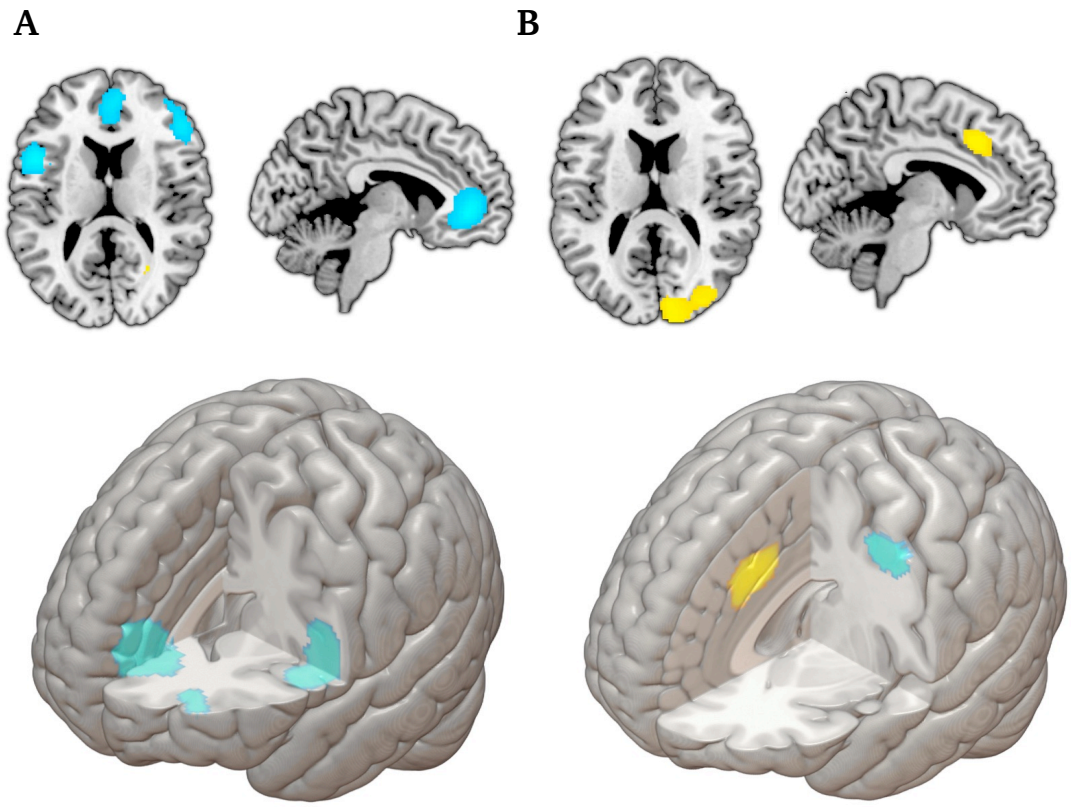
Missing data coded (-): PTSD, post-traumatic stress disorder: OCD, obsessive compulsive disorder: (g)SAD, (generalized) social anxiety disorder: PD, panic disorder: Tc-99-ECD SPECT, technetium-99m-ethyl cysteinate dimer single photon emission computed tomography: fMRI, functional magnetic resonance imaging: DSM, Diagnostic and Statistical Manual of Mental Disorders: LSAS, Liebowitz Social Anxiety Scale: YBOCS, Yale-Brown Obsessive Compulsive Scale: CBT, cognitive behavioural therapy: CAPS, Clinician-Administered PTSD Scale for DSM: ACT, acceptance and commitment therapy: ACQ, Agoraphobia Conditions Questionnaire: BATD, Behavioural Activation Therapy for Depression: MDD, major depressive disorder: BDI, Beck Depression Inventory.

Table 2-f: Regions significantly predicting symptomatic improvement

Regions	Peak MNI coordinate	SDM Z-value	*p*	Number voxels	BA
Increased activity associated with greater symptomatic improvement					
Right cuneus cortex[1]	10, -92, 14	1.74	0.0004	1066	18
Left median cingulate / paracingulate gyri / left anterior cingulate[2]	-4, 26, 36	1.81	0.0002	411	24
Right frontal orbito-polar tract[3]	20, 36, -14	1.66	0.0007	96	-
Decreased activity associated with greater symptomatic improvement					
Left precentral/postcentral gyrus[4]	-44, -2, 52	-1.09	0.0003	326	6

MNI, Montreal Neurological Institute; SDM, seed-based d mapping; BA, Brodmann Area. **[1] Driven by Doehrmann et al. (2013) only. [2] Not significant when Carl et al. (2016) and Klumpp et al. (2016) were excluded. [3] Not significant when Klumpp et al. (2014) and Yamanishi et al. (2009) were excluded. [4] Not significant when Klumpp et al. (2014) and Olatunji et al. (2014) were excluded.**

Figure 2-b: A) Results of longitudinal meta-analysis showing brain activation changes pre-to post- psychological therapy; B) Results of prediction meta-analysis, pre-treatment activation associated with subsequent symptomatic improvement



Blue areas denote regions where there was decreased activation – in Figure 2A) decreased activation post- versus pre-therapy and in Figure 2B) lower baseline activation associated with greater symptomatic improvement. Yellow areas denote regions where increased activation was found – in Figure 2A) increased activation post-versus pre-therapy and in Figure 2b) higher baseline activation associated with greater symptomatic improvement.

2.4 Discussion

These meta-analyses examined changes in brain activation associated with psychological therapy and neuroimaging predictors of subsequent treatment response in both depression and anxiety disorders. Since the publication of similar reviews and meta-analyses in this field (for example, (Fu et al., 2013; Lueken & Hahn, 2016; Messina et al., 2013) there have been a considerable number of new publications. We used an improved analysis method which has various strengths compared to other neuroimaging meta-analytical techniques (Radua et al., 2014). We implemented a thorough and conservative approach to identify only the most robust findings within this heterogeneous literature and papers were assessed for suitability more rigorously than previous reviews to ensure that only papers reporting whole brain data were included.

2.4.1 Longitudinal findings

The most robust findings were that psychological therapies resulted in decreased activation, post- compared to pre-therapy, in clusters with peak co-ordinates in the left ACC, inferior frontal gyrus (bilaterally) and left insula. It is important to note that studies had typically included both responders and non-responders in their analyses and therefore the changes are not indicative solely of treatment response. Due to our jackknife analyses, which indicated evidence of consistency in the findings across studies, the results appear to show brain activation changes which are consistent across psychological therapies and are trans-diagnostic. However, it is important to highlight that these findings do not signify that there are not changes in activation that are specific to types of psychological therapy or able to differentiate between disorders and their subtypes. There were currently, however, too few studies to study disorder- or treatment-specific brain activation changes via meta-regressions. Additionally, it would be difficult to

confidently study one disorder in isolation from another due to high levels of comorbid Axis I disorders in the patient samples (see Table 2-a).

The meta-analyses were run separately on task and resting-state studies due to evidence that paradigm type can substantially effect results (Fu et al., 2007; Messina et al., 2013; Palmer et al., 2015; Whitfield-Gabrieli et al., 2011). Our subgroup analysis revealed substantial differences between these paradigms, highlighting the importance for future reviews in this field to consider the two separately.

A decrease in ACC activity post-therapy was a common finding across both resting state and activation paradigms. This result is in agreement with a recently published systematic review on brain activation changes with CBT, which summarises that the most consistent finding is decreased dACC activity (Franklin et al., 2016).

As with the Messina meta-analysis, we did not find dlPFC involvement despite this region being associated with attentional control and emotional regulation (Hofmann et al., 2012; Kane & Engle, 2002; Owen et al., 2005; Wager & Smith, 2003). This could be due to an insufficient number of studies in our meta-analyses to demonstrate this effect and an inconsistency between the designs of included studies. We did find significant effects elsewhere in prefrontal brain regions which suggests that involvement of the PFC in affective disorders may be complex and not attributable to a single region as has been suggested previously (Fitzgerald et al., 2006; Thomas & Elliott, 2009).

2.4.1.1 Implications for the dual process model

If psychological therapies were to normalise top-down prefrontal control as hypothesised in the dual process model, one would expect increased activity in prefrontal regions and consequently to this, decreased activity in the limbic network. The decreased activation we found in limbic regions (the left ACC and left insula) is consistent with this emotional

regulation model of depression and anxiety. However, the decreased activation we found bilaterally in the inferior frontal gyrus runs counter to this, as the theory proposes increased activation in pre-frontal regions.

Despite these findings being at odds with the model, they do not necessarily undermine its credibility. Decreased prefrontal activity, particularly in resting-state studies, may signify an enhanced capacity for top-down regulation when required i.e., these areas were dysregulated but regained the capacity to respond appropriately and are 'better' utilised when necessary after psychological therapy.

The dual process model is appealing due to its parsimony and fitting with the theoretical modes of action we would expect from treatments for affective disorders. For example, CBT is proposed to improve emotional regulation by challenging negative cognitions and improving conscious emotional regulation. We would therefore expect greater cognitive control to be evident in prefrontal conscious emotional-regulation brain regions. However, the model may be too simplistic as it ignores any compensatory changes in functioning that may be occurring. This more complex model has been proposed by Willner et al. (2013) in relation to the mode of action of antidepressants, but we suggest that there are also likely to be compensatory, as well as normalising, mechanisms involved with psychological therapies.

Additionally, it is unlikely that the effects of psychological therapies can be solely represented by cognitive control and voluntary emotional regulation with a linear relationship between prefrontal and limbic regions. Messina et al. proposed an alternative neural model of action of psychological therapy, albeit with a focus on psychodynamic therapy models (Messina et al., 2016). They highlighted that the dual process model ignores that psychodynamic therapy aims to regulate emotional states, not only by strengthening executive control but through the resolution of early childhood parental

interactions and challenging negative representations of the self and others in relationships. They therefore postulated that one should expect direct changes in DMN and implicit emotional regulation regions which are involved in self-referential processing. Their model may also be applicable to other psychological therapies which place importance on directly challenging negative self-views.

2.4.1.2 Comparison to antidepressants

Psychological therapy is vastly understudied compared to the neural correlates of antidepressant medication. Ma (2015) conducted a meta-analysis of the neural correlates of antidepressants which included 60 studies (n=1,569). They found decreased activation in the ACC, amygdala and thalamus and increased activation in the dlPFC with antidepressant medication. Their results therefore fit well with the dual process model which hypothesises that antidepressants act more directly on the emotional, limbic network whereas psychological therapies primarily target prefrontal function by increasing inhibitory executive function. However, we found evidence of reduced activation in the emotional network with psychological therapies and therefore differentiation between treatment modalities may be more complex than proposed in the dual process model. It could be that, rather than results reflecting the effects of specific therapies, findings reflect processes of recovery more generally. Further studies directly comparing treatment modalities are required to explore how far changes reflect general as opposed to treatment-specific modes of recovery. A meta-analysis comparing treatment modalities would also be beneficial in this regard. Studies with a more frequent follow up throughout the course of treatment would enable us to more rigorously test the dual process model to see if there is a differential primary action between treatment modalities. Additionally, work using dynamic causal modelling of fMRI data or transcranial magnetic stimulation (TMS) could further allow us to determine the causal direction of results.

2.4.2 Prediction findings

In terms of the prediction data, our analyses show there to be inconsistency between study results and too few published studies at present to determine robust predictors of symptomatic improvement with psychological therapy. Speculatively, this could imply that prediction is more disorder or treatment specific. We found one area, the right cuneus cortex, whose greater activation at baseline was associated with greater symptomatic improvement. This extrastriate region has been implicated in response inhibition, in particular those involving motor reactions (Booth et al., 2005; Matthews et al., 2005). The cuneus forms part of the DMN, and has been found to be abnormally activated in depression (Greicius et al., 2009). In a study included in these meta-analyses on the neural correlates of mindfulness-based stress reduction, the authors speculated that their observed increase in cuneus activation post-therapy could be due to the patients being less visually avoidant of negative self-beliefs and imagery, or alternatively reflect patients engaging in enhanced visual attention during scanning post-treatment (Goldin & Gross, 2010).

We hypothesised that increased baseline ACC activation would be associated with symptomatic improvement, in line with previous reviews (Fu et al., 2013, Lueken & Hahn, 2016). We did find that elevated left ACC activation was associated with greater symptomatic improvement; however, this region did not meet our criteria for robustness. Our failure to find this robustly could be due to the small number of studies included in this analysis and between study heterogeneity. Indeed, Lueken and Hahn 2015 note in their systematic review that the direction of predictive effects of anterior cingulate activity was dependent both on the type of functional imaging paradigm used and the specific psychological treatment received. Therefore, anterior cingulate activation could have been masked in this meta-analysis by cancelling out both positive and negative effects

found in this brain region. Currently, however, there were too few studies to allow exploration of the effects of task on this analysis.

2.4.3 General strengths and limitations of the meta-analyses

Although these meta-analyses present a comprehensive summary of the evidence base so far in this field, the results should be considered cautiously. The present literature is small meaning the influence of between study heterogeneity, other than paradigm type, could not be assessed through meta-regressions.

Between-study heterogeneity could have influenced the results of these analyses in several ways. Firstly, all functional neuroimaging designs were included ranging from resting-state to emotionally distressing or cognitively demanding tasks. Although we did control for resting-state versus task-based methodology to increase specificity in findings, even the type of task can have a great effect on the neural activation detected (Fu et al., 2007; Palmer et al., 2015). However, by adopting inclusive eligibility criteria for paradigm type, this will have increased power given the paucity of research in this field and allowed greater generalisability of global results to broad neurobiological models. Secondly, the included studies comprised patients with a range of disorders, comorbidities, and symptom severity, another source of within-study variability. Thirdly, we would expect that the specific neural changes occurring with therapy would differ according to the type of psychological therapy the patient received (for example, as has been found with studies directly comparing different therapies (Burklund et al., 2017; Månsson et al., 2013). Finally, we included SPECT, PET and fMRI scanning methodologies. These methods differ in their measurement of brain activity, temporal and spatial resolution. Therefore, it is plausible that findings from the various modalities could differ considerably. However, all included PET and SPECT studies used radiotracers to

measure regional brain glucose metabolism, which is the measurement most related to fMRI BOLD signal. Additionally, we only included studies where participants fulfilled full diagnostic criteria. Although warranted, given the scope of these meta-analyses, the results may not be generalisable to those individuals who evidence subthreshold clinical anxiety or depression.

Despite considerable heterogeneity in study designs which these meta-analyses illustrate, patients in the included studies were typically in the moderate to severe range of severity, most therapies were cognitive and/or behavioural in nature, and a negative emotional scanning paradigm was primarily used. Commonalities did emerge, and we were able to demonstrate some consistent findings.

Another limitation is that we only included results of the patient group who received therapy. Care should be taken when considering the results of these meta-analyses, and indeed studies in this area, as effects are unlikely to be solely attributable to the treatment under investigation and may in part be due to spontaneous remission or concomitant therapies. This problem could be ameliorated by the inclusion of a placebo arm (for example, in the case of psychological therapy, one-to-one non-therapy sessions or wait-list control groups). Although fully balanced designs, with control groups who also receive scans at both time points, are best practice in order to appropriately model the effect of repeated scans and other non-treatment related factors (Dichter et al., 2012), including only these studies was not within the capacity of these meta-analyses in order to maximise the number of suitable studies. Many studies had either not included a control group or had scanned controls only once at baseline.

Additionally, as with all meta-analyses, the potential influence of publication bias should be considered when interpreting the results. Although, in our longitudinal meta-analysis, we did not show any evidence of this, there were signs of publication bias in the prediction

of treatment response meta-analysis. Also, our reliance on including only peak co-ordinates reported in published papers does not provide the level of detail that statistical parametric maps or individual-level data would. Indeed, if a study did not find any significant whole brain results, they were assumed to have an effect size of 0 which may not be justified.

2.4.4 Overall conclusion

In conclusion, our meta-analyses provide a summary of the evidence to date. Although the literature is relatively small, there do appear to be some consistent brain activation changes with psychological therapy across depression and anxiety disorders. However, neural changes that are robustly predictive of treatment response remain elusive. We suggest that more research is required to form definitive conclusions in order to benefit patients at an individual level by tailoring treatment according to likely response and understanding treatment mechanisms in order to improve treatments.

Chapter 3: General Methodology

3.1 Study designs

This work included two pilot studies to assess the utility of novel methods to assess self-reflection and threat avoidance in depression and anxiety:

Study 1 – An MRI study where patients, with major depression and varying degrees of clinical anxiety, and healthy controls completed a series of structural and functional brain scans including the Joystick Operated Runway Task (JORT) and Fake IQ test. Participants also completed the JORT and Fake IQ test offline (i.e. outside of the scanner).

Study 2 - A behavioural study where participants completed the JORT and Fake IQ test offline before and after a course of CBT to determine associations between task performance and treatment response.

3.2 Participants

Study 1

40 right-handed participants aged 18-65 years were recruited from the community in South London via waiting lists of local psychological therapy services and using online advertisements (the utility of various recruitment methods in this study has been published, see Wise et al., (2016)). See Table 3-a for participant characteristics.

Table 3-a: Participant baseline characteristics, Study 1

	Patients (n=20)	Controls (n=20)	Group comparison
Age (years)	31.6 (10.4)	31.6 (10.0)	t = .015
Gender (F/M) (n)	13/7	13/7	$\chi^2 = 0$
Ethnicity (white /black /Asian or other) (n)	13/2/5	14/5/1	$\chi^2 = 4.0$
Employment status (full-time/part-time/ unemployed / student) (n)	2/2/10/6	8/6/1/5	$\chi^2 = 13.1$*
BMI (kg/m2)	23.7 (4.9)	25.4 (5.2)	t = -1.0
HDRS-17	19.2 (3.6)	1.0 (1.4)	t = 21.0**
HARS	23.0 (5.9)	1.0 (1.2)	t = 16.4**
Number previous episodes (median, interquartile range)	4 (3)	N/A	-
Current episode duration (months)	20.0 (26.3)	N/A	-
Current episode failed adequate antidepressant treatment trials (n)	5 (4 participants with 1, 1 participant 2)	N/A	-
Comorbidities (n)	Total with 1(+) comorbidity: 13. GAD (9), OCD (3) PTSD (2), (g)SAD (6), PD (1)	N/A	-

Results are reported as mean (standard deviation) except where otherwise stated. **** p<.05, ** p <.0001. Abbreviations - F, female; M, male; BMI, Body Mass Index; HDRS, Hamilton Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale; GAD, Generalised Anxiety Disorder; OCD, Obsessive Compulsive Disorder; PTSD, Post-traumatic Stress Disorder; (g)SAD, (generalised) Social Anxiety Disorder; PD, Panic Disorder (with or without agoraphobia).***

At study entry, all patients met current DSM-IV criteria (American Psychiatric Association, 2013) for major depressive disorder or episode, as determined by clinical interview based on the Mini International Neuropsychiatric Interview, Version 5.0 (MINI 5.0) (Sheehan

et al., 1998). Co-morbid Axis I anxiety disorders, as diagnosed by the MINI 5.0, were allowed alongside major depression. Depression severity was assessed using the 17-item Hamilton Depression Rating Scale (HDRS-17, Hamilton, 1960) and a score of 14 or greater required for inclusion. A diagnosis of bipolar disorder (I or II) or current psychosis (assessed using the MINI 5.0), borderline personality disorder (determined via the Structured Clinical Interview for DSM-IV Axis II disorders (First & Gibbon, 2004) or self-report of a formal diagnosis by a psychiatrist) were exclusion criteria.

Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). Patients were not receiving any form of treatment (psychotropic or psychological) at the time of scanning and had been psychotropic medication-free for at least 8 weeks prior to inclusion. Age, gender and handedness matched healthy controls were assessed to exclude personal and familial (first-degree relative) psychiatric history.

All participants were required to have no neurological disorders, for example dementia, known cerebral lesions, head trauma resulting in loss of consciousness, learning disabilities e.g. dyslexia, or un-correctable visual problems. Additional exclusion criteria for all subjects included illicit substance use in the preceding two months, no current (within 12 months of study entry) alcohol or other substance abuse (as determined via the MINI 5.0), unstable or severe medical conditions, any treatment with potential psychotropic properties or interference with participants' safety or data interpretation, pregnancy, or other contraindications for scanning.

Study 2

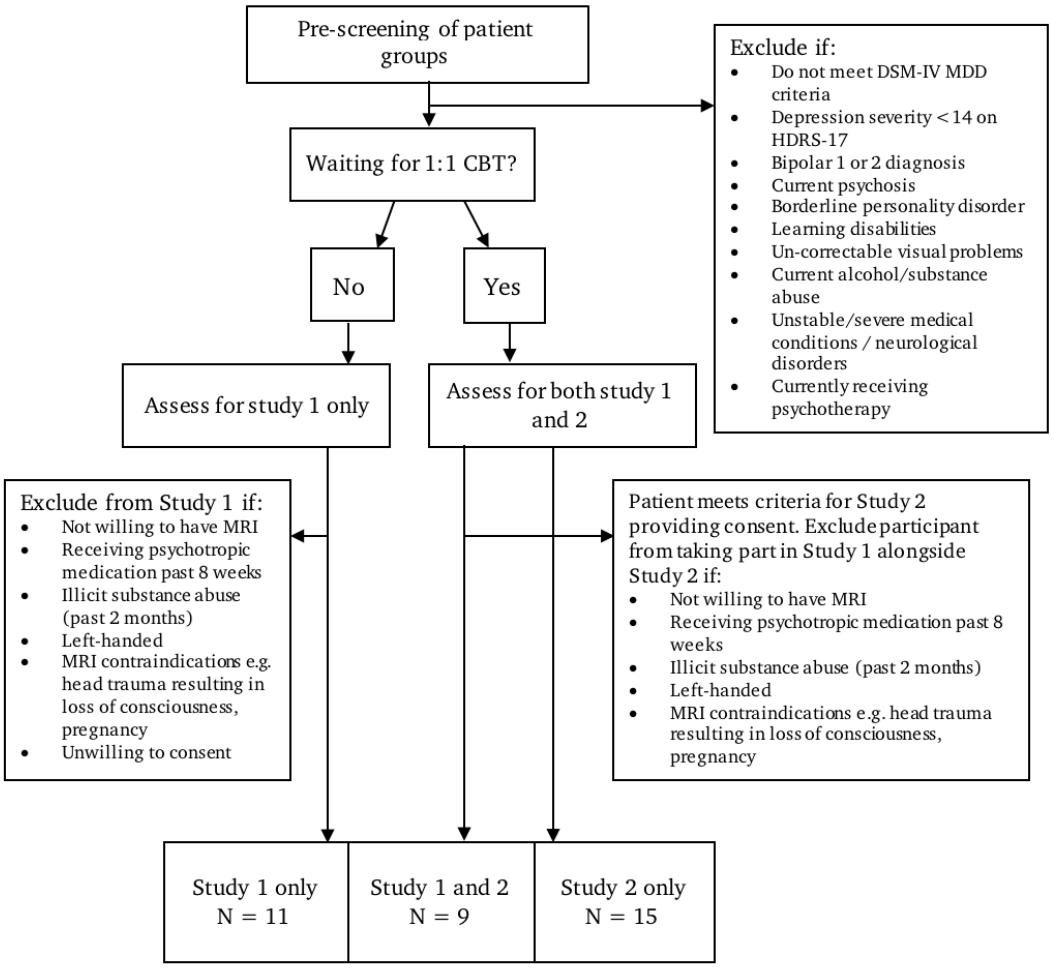
The above inclusion criteria applied to patients entering the behavioural arm of the study with the exception that current psychotropic medication did not exclude participants, nor did left-handedness. An additional inclusion criterion for behavioural participants was the

requirement for patients to be waiting for, but not yet started, one-to-one CBT. All participants were followed up as close as possible after completing their course of CBT.

Recruitment to the two studies happened in parallel. Participants in Study 1 completed the Fake IQ test and JORT offline as well as in the scanner and therefore 9 participants from Study 1 are also included in Study 2 as they were waiting for a course of CBT at the time of enrolling in the study and subsequently completed a course of CBT (see Figure 3-a for flow chart of patient recruitment into the two studies).

24 participants were recruited into the behavioural arm of the study (mean age 36.28 ± 13.12 years, 15 females). See Table 3-b for participant characteristics. Twenty-two participants completed a course of CBT with their local Improving Access to Psychological Therapies (IAPT) service, one participant with a Community Mental Health Team, and another with their University counselling service. The number of sessions of one-to-one CBT that participants received varied greatly, ranging from 6 to 28 sessions (mean 11.6+-5.0). NICE guidelines state that patients receiving high intensity CBT should typically receive 16-20 sessions over 3-4 months (NICE, 2009). The guidelines also state that for those with mild to moderate depression (the mean HDRS-17 score of this sample is in the moderate range (Zimmerman et al., 2013)), 6-8 sessions should be sufficient delivered over 9 to 12 weeks. Therefore, all patients included met the minimum criteria of 6 sessions according to NICE guidelines; however, for some patients the CBT they received may have been suboptimal according to recommended guidelines dependent on their severity.

Figure 3-a: Flow chart of patient recruitment to Studies 1 and 2



Abbreviations – MRI, Magnetic Resonance imaging; DSM-IV, Diagnostic and Statistical Manual, 4th Edition; MDD, Major Depressive Disorder; HDRS-17, 17 item Hamilton Depression Rating Scale.

Table 3-b: Participant baseline characteristics, Study 2

	Patient (n=24)
Ethnicity (white /black /Asian or other) (n)	16/1/7
Employment status (full-time/part-time/ unemployed / student/retired) (n)	7/4/8/4/1
BMI (kg/m2)	24.87 (4.89)
HDRS-17	19.46 (4.23)
HARS	24.63 (7.94)
Number previous episodes (median, interquartile range)	4 (4)
Current episode duration (months)	33.90 (40.62)
Current episode failed adequate antidepressant treatment trials (n)	11 (7 participants with 1, 3 participants with 2 and 1 participant with 4)
Comorbidities (n)	GAD (10), OCD (2), PTSD (4), (g)SAD (12), PD (10)
Currently taking psychotropic medication	8
Length of CBT (number of sessions)	11.6 (5.0) Range: 6-28
Responders (MÅDRS >=50% reduction) (n)	10
Remitters (MÅDRS score of 7 or less post-therapy) (n)	5

Results are reported as mean (standard deviation) except where otherwise stated.

Abbreviations - F, female; M, male; MÅDRS, Montgomery Åsberg Depression Rating Scale; HDRS, Hamilton Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale; GAD, Generalised Anxiety Disorder; OCD, Obsessive Compulsive Disorder; PTSD, Post-traumatic Stress Disorder; (g)SAD, (generalised) Social Anxiety Disorder; PD, Panic Disorder (with or without agoraphobia).

3.3 Ethical approval

Ethical approval was granted by the London-Bromley Research Ethics Committee (reference: 13/LO/1897) and R&D approval received from the South London and

Maudsley NHS Foundation Trust (reference: R&D2014/011). All participants provided informed written consent and received financial compensation for taking part.

3.4 Study procedures

The participants involved in Study 1 completed all measures that participants in Study 2 did but with the addition of fMRI. Participants attended the following study visits:

1) Screening assessment to determine eligibility and baseline visit
2) fMRI scan for participants in Study 1 (in Study 2, a course of CBT though nine participants from Study 1 were also included in Study 2 due to receiving CBT)
3) Follow-up (post-CBT in Study 2 patients and in Study 1 participants after a similar length of time if not receiving CBT, mean =15.6 +- 6.6 weeks)

In addition to the MINI 5.0 and HDRS-17 to determine eligibility, participants completed the following clinical assessments at baseline and follow-up:

- The Hamilton Anxiety Rating Scale (HARS): a 14-item clinician-rated measure of anxiety severity. Items, including psychic and somatic anxiety symptoms, are rated on a 5-point scale from 0 (not present) to 4 (severe) (Hamilton, 1959).
- The Montgomery-Åsberg Depression Rating Scale (MÅDRS): a clinician-rated 10-item measure of depression severity with each item rated from 0-6, higher scores indicating greater severity (Montgomery & Asberg, 1979). Response to therapy was defined using the widely accepted criteria of a 50% or greater reduction in MÅDRS scores (post- compared to pre-therapy) and remission defined as a post-treatment MÅDRS score of seven or less (as found by Riedel et al., 2010 to be the best definition of remission). As is best practice, a different measure of symptom

severity was used for inclusion (the HDRS-17) and response (the MÅDRS). The MÅDRS was selected as the measure for response and remission as it has been shown to have a better sensitivity for detecting symptom change than other measures of depression severity (Montgomery & Asberg, 1979).

3.5 Scanning procedure and methodology

In Study 1, structural and functional images were acquired on a 3-Tesla GE MR750 scanner (GE Medical Systems, Milwaukee, Wisconsin) with a 12-channel radiofrequency head coil at the Centre for Neuroimaging Sciences, King's College London. The structural sequence comprised a high-resolution sagittal Magnetisation Prepared Rapid Acquisition GRE 3D Inversion Recovery (MP-RAGE) anatomical reference image: inversion time = 400 milliseconds (ms); echo time (TE) = 3.016 ms; repetition time (TR) = 7.312 s; flip angle 11°; slice thickness = 1.2 mm (196 contiguous slices). These T1-weighted gradient echo structural images were normalised and segmented into grey matter, white matter, and cerebrospinal fluid. Images were inspected for artefacts, for example motion and inhomogeneity, before and after normalisation.

Before scanning, participants underwent a session in a mock MRI scanner to explain and demonstrate the equipment to be used, including a head coil and scanner sounds presented through headphones to acclimatise participants to the scanning environment. Studies have shown that familiarising patients with the scanning environment in a sham scanner reduces anxiety during scanning (Rosenberg et al., 1997). This was therefore especially important in our patient population where problems, for example, claustrophobia and panic symptoms, may have been magnified.

After the structural scan, participants completed three functional scans (as detailed in Table 3c). Functional MRI is a technique for measuring haemodynamic changes resulting from neural activity in the brain, an indirect measure of brain activation. The tasks reported in this thesis measured functional activation via blood-oxygen-level-dependent (BOLD) signals. BOLD signal is linked to brain activation as blood releases oxygen to active neurons at a greater rate than inactive neurons, a process called haemodynamic response (Ogawa & Lee, 1990; Ogawa et al., 1990). The level of oxygenated and deoxygenated haemoglobin affects the signal strength in MRI due to their different magnetism.

Table 3-c: fMRI task parameters

Task Name	**MULTI-ECHO RESTING STATE**	**JORT**	**Fake IQ Task**
fMRI task order	1st	2nd	3rd
Number of slices	33	41	41
Slice thickness / gap (mm)	3.8/0/4	3/0.3	3/0.3
Area of brain to be covered	Whole brain	Whole brain	Whole brain
FOV (cm^2)	24	24	24
TR (ms)	2300	2000	2000
TE (ms)	12.7/31/48	30	30
Flip Angle (degrees)	75	75	75
Number of images per location	540	180	338
Total scan time (mins)	08:15	18:14	11:17

Abbreviations - JORT, Joystick Operated Runway Task; FOV, field of view; TR, repetition time; TE, echo time; fMRI, functional magnetic resonance imaging.

In addition to the functional imaging tasks, where BOLD signal is measured over the course of a specific task, participants completed a resting-state scan. Paradigm free, or resting-state, imaging studies allow functional connectivity correlations in Blood Oxygen Level Dependent (BOLD) signal in time series to be explored (Biswal et al., & Hyde,

1995). These studies have been key in identifying functional networks between brain regions i.e., areas that are spatially dispersed but functionally correlated (Cordes et al., 2000; Greicius et al., 2003). The large-scale patterns of correlated activity between distant brain regions, so called networks due to the assumption that they have physical connections, reveal neural systems that have coherent activity over time and which are thought to demonstrate distinct cognitive functions (Bullmore & Sporns, 2009; Fox & Raichle, 2007; Honey et al., 2007; Smith et al., 2009). These connectivity signals have been found to be related to neural activation and structural connectivity, and therefore are unlikely to simply result from noise in the data (Bullmore & Sporns, 2009; Fox & Raichle, 2007; Honey et al., 2007; Smith et al., 2009). In comparison to functional connectivity which infers connectivity through correlations in brain activity, structural connectivity maps anatomical white matter tracts between brain regions using methods such as diffusion imaging (Gong et al., 2009).

Resting state analysis was also conducted in an independent validation sample of participants with major depression recruited into a separate study. Ethical approval and funding for this separate study was granted by the Bromley NHS Research Ethics Committee. All subjects provided written informed consent and were compensated financially for taking part in the research. This study was funded by an Academy of Medical Sciences grant (grant code: SGCL8).

This sample included right-handed patients with unipolar depression and healthy controls, matched by age, sex and handedness. As with Study 1, all patients met DSM-IV current criteria for major depression, determined by clinical interview with a psychiatrist using the MINI 5.0 (Sheehan et al., 1998) and had a minimum score of 18 on the MÅDRS (Montgomery & Asberg, 1979) (all participants in Study 1 also met this severity criteria). To ensure inter-rater reliability between the samples' raters, the two raters were trained

on an independent sample of patients and showed high levels of inter-rater reliability on the MÅDRS (intraclass correlation coefficient = 0.96, p = .004).

Unlike in Study 1, where comorbid anxiety disorders were allowed alongside major depression, comorbid conditions were excluded in this validation sample. Additionally, patients were excluded if they reported any illicit substance use in the previous two months, had any physical health conditions or took any medication that could result in psychiatric symptoms.

As with Study 1, patients in Sample B were recruited from the South London area through public advertisements and from wait-lists of local psychological therapy services (Wise et al., 2016). All patients were medication-free for at least 2 weeks (4 weeks for fluoxetine) before scanning and were not currently undergoing any psychological therapy. Healthy control participants were recruited from the community using online advertisements, and reported no current or past psychiatric diagnoses, and no history of psychiatric illness in first-degree relatives. Participants reporting history of head injury, major medical illness, pregnancy or any other contraindications for scanning were excluded.

3.6 Statistical analysis

Behavioural data were analysed using SPSS Version 24.0 (SPSS Inc. Chicago, US). Group differences were assessed with independent-samples t-tests for continuous data and chi-square tests for categorical data. Analyses of the associations between CBT and task measures or questionnaire ratings were conducted using repeated measures ANOVAs to determine if these measures are associated with differences pre- to post- therapy between treatment responders and non-responders. This type of responder versus non-responder

analysis was chosen over continuous measures of symptomatic change as it is clinically useful to know if the measures are associated with response.

In fMRI analyses, multiple comparisons were corrected for and only brain regions surviving multiple corrections, or a predefined limit on cluster-size, are reported as definite results. Findings are reported throughout this thesis in standard Montreal Neurological Institute (MNI) anatomical space.

Chapter 4: The Fake IQ test: a novel, direct measure of self-reflection in major depression and anxiety[1]

Chapter Summary

Excessive negative self-referential processing is a common feature of psychiatric disorders, yet discerning whether it is a cause or effect of illness remains a challenge as the tools available for measuring self-reflection are limited to self-report questionnaires or reliance on invoking emotional states. Here we present an objective measure of self-reflection, the Fake IQ Test. This computerised task measures self-reflection by presenting participants with sets of items that are described to them as testing an intelligence construct known as "visual perception ability". This construct is fictitious and after each set of items, participants are asked to estimate their total number of correct answers, whether their performance was better or worse than average, and whether they were satisfied with their performance. The design of the task's items means there are no right or wrong answers and so perceived differences in performance between subjects reflect individual differences in self-perception.

We piloted the Fake IQ test in patients with major depressive disorder and comorbid anxiety and healthy controls as an fMRI and behavioural task. Behaviourally, 30 patients

[1] The behavioural results in this chapter, comparing patients versus controls performance on the Fake IQ test have been adapted from the following publication on which I am joint first author: Patrick, F., Marwood, L., Corfield, F., Cardi, V., Cleare, A. J., & Perkins, A. M. (Under Review). The Fake IQ Test: an objective measure of self-criticism.

and 20 healthy controls completed the task. We found elevated negative self-comparison to others, higher self-dissatisfaction, and lower perceived success in depressed patients relative to controls on the task. A subset of patients (n=15) completed the task both before and after a course of cognitive behavioural therapy to determine associations between this measure and treatment response. Therapy responders were not found to have significant differences in task subscale scores compared to non-responders at either baseline or post-therapy assessment. Additionally, there were no significant differences over time, pre- to post- therapy, on any of the task's subscales.

Thirty-five participants completed the Fake IQ test during MRI scanning (16 patients and 19 healthy controls). A main effect of task was found with greater activation in self-reflection versus control conditions bilaterally in the inferior frontal cortex, insula, dorsolateral prefrontal cortex, motor cortex and dorsal anterior cingulate cortex. However, there were no significant differences between patients versus controls in neural activation on the task, nor correlations between brain activity and measures of self-reflection.

Additionally, no relationship was found between scores on the FIQT and questionnaire measures of self-reflection in behavioural testing, suggesting the FIQT measures an aspect of self-reflection inaccessible to current questionnaires. We therefore propose the FIQT as an alternative to traditional self-report measures of self-reflection, with application to multiple patient groups and experimental paradigms, including drug and tentatively neuroimaging studies. Future work should study the task in a variety of psychiatric disorders associated with aberrant self-reflection, using larger sample sizes.

4.1 Introduction

As described in the introductory chapter (Chapter 1), maladaptive self-reflection appears as a key feature in mental health pathology. Self-reflection can be considered as a spectrum, ranging from pathologically negative and elevated levels in MDD, anxiety and eating disorders (Blatt, 2004; Dunkley & Grilo, 2007) through more positive and normal levels of self-reflection (for example, self-reassurance and compassion) observed in healthy populations (Bradley et al., 2016), to diminished levels in conditions such as autism and schizophrenia (Philippi & Koenigs, 2014).

Self-reflective cognitions are often assessed via global self-report measures, such as the Forms of Self-Criticising/Attacking and Self-Reassuring Scale (Gilbert et al., 2004). These relate to general experiences without contextual definitions (e.g. "I find it difficult to control my anger and frustration at myself"). A concern with self-report questionnaires is the potential for self-bias (Iancu et al., 2015) and due to their reliance on semantic, autobiographical memory, their output is dependent on accessible memories which may be influenced by personal expectations and beliefs (Rosenberg et al., 2016). These measures may be particularly inaccurate and insensitive to change in clinical populations with decreased insight as they depend on awareness of the reported cognitions (Offer et al., 2000; Orfei et al., 2008; Reuben et al., 1992).

Concerns surrounding measurement of self-reflective behaviours and thoughts are particularly compounded when assessed in neuroimaging studies, as their paradigms often involve the participant engaging in imaginative states of self-referential thought. The most widely used neuroimaging task to measure self-reflection is trait personality judgement where participants consider the degree to which statements of personality apply to themselves or others. These studies, which again rely on insight, have identified that activity in the mPFC (D'Argembeau et al., 2005; Macrae et al., 2004; Moran et al.,

2006) and PCC (Moran et al., 2006) are associated with the level of self-relevance during personality judgement. Other similar fMRI tasks include the participant considering the self-relevance of positive, negative and neutral statements, similar to those in global self-report questionnaires, designed to cue self-referential processing, for example “I consider myself to be a loser” (Wagner et al., 2015). Those with an even greater imaginal element include, for example, a study by Longe et al. (2010) which asked participants to imagine being either self-critical or self-reassuring to scenarios of personal failures and mistakes during scanning. They found that activity in the dorsolateral PFC, hippocampal and amygdala complex were positively correlated with an individual's tendency to be self-critical, whereas insular, ventrolateral and ventromedial PFC activity were positively correlated with the tendency to be self-reassuring. Another similar task involved participants imagining their hopes and aspirations (self-reflective condition) versus duties and obligations (comparative self-evaluative condition) (Johnson et al., 2009).

These neuroimaging measures rely on the assumption that internally imagined states are equivalent to those produced by external stimuli through a specific task. Whilst there is some evidence of an overlap between real and imagined states, the validity of this design has been brought in to question (Klein & Gangi, 2010; Prigatano & Fordyce, 1986) and there are likely to be confounds of individual differences in a person’s ability to realistically imagine certain states. In addition, tasks which involve actively encouraging depressed participants to be self-critical, ruminative and self-blaming may be unethical. A further issue with those tasks involving a self-reassuring element is that they may not be suitable for certain patient groups. Indeed, when a highly self-critical individual is asked to be self-reassuring, they have been found to respond with threat-like responses (Rockliff et al., 2008) and patients with depression have been found to have deficits in self-soothing even when remitted (Ehret et al., 2015; Hooley et al., 2005).

In addition to these issues, there is a cause and effect confound in the relationship between adverse events, psychiatric illness and negative forms of self-reflection. This confound arises because excessive negative self-reflection may cause psychiatric illness but may also be a consequence of adverse life events (Monroe & Simons, 1991). Attempts to clarify whether excessive self-criticism causes psychiatric illness may therefore be hindered by the inability of current measures to distinguish between endogenous self-criticism (i.e., a trait tendency or genetic predisposition) and exogenous, situationally-driven self-criticism that stems from stressful life events (e.g., childhood trauma or sexual abuse).

A potential solution to the inherent problems with measures of self-report and imagined internal states is to use more implicit measures whereby the task automatically induces and directly measures aspects of self-reflection. One way of approaching this would be to present participants with a task that they believe to be real test of ability, but on which all participants perform the same. This task would have three advantages over conventional measures of self-reflection. First, it removes the need for participants to imagine themselves in an evaluative context, because it *is* an evaluative context. Second, because all participants perform the same, their perceptions of their performance reflect individual differences in self-reflection rather than the effect of other attributes. Third, because the task elicits self-reflection, life history differences are somewhat controlled for between participants. These three features mean that such a task would be better suited to measuring endogenous negative self-reflection than existing questionnaires.

The Belgian child psychologist Joseph Nuttin attempted to achieve this goal in a series of experiments which portrayed tasks as tests of intelligence, but were in reality implicit measures of self-perception (Nuttin & Greenwald, 1968). In one experiment, participants were asked to estimate which of two shapes presented together on one card was larger.

Participants were told that they had performed equally as well as one another with feedback based on a pre-defined schedule rather than actual performance. After completing the series, participants were asked: 1) how many times they thought they had been told that they were correct and incorrect; and 2) asked if they were satisfied with their performance. When Nuttin's participants were split in to 'pessimists' and 'optimists', and in a second experiment, 'depressives' and 'manics'; in both cases, the former grouping was more likely to overestimate failures. This backs up other evidence suggesting that correlations between perceived and actual success is low (Hilgard & Sait, 1941). These findings show that individuals perceive successes and failures in the context of a pre-established conception of the self, independent of actual task performance and feedback received (Nuttin & Greenwald, 1968).

Perhaps because of a lack of exposure in English-language publications, despite its promising application, Nuttin's task has been largely neglected for the past 50 years. We have created an improved computerised version, called the Fake IQ Test (FIQT), to test the utility of this measure in a modern psychiatric context due to the task's suitability to be utilised in various clinical populations including those with special requirements (for example, young children) and across various study paradigms. We have added a third question, probing how well individuals believe they have performed compared to peers; an important consideration, as research has indicated that self-criticism may arise from combined self-disapproval and chronic fear of criticism from others (Blatt, 2004). An additional improvement is our removal of task feedback, which could differentially influence affect and subsequently perceived performance (Besser et al., 2004; Elliott et al., 1996).

Other tasks have gone some way to achieving this goal of creating a direct measure of self-reflection. For example, a Cyber Ball Task which manipulates the amount of exclusion

a participant experiences in a virtual ball passing game (van Harmelen et al., 2014). Participants are asked questions about self-esteem after completing the task to measure sensitivity to social criticism which the experiment manipulates by the number of rejections the participant experiences. The FIQT is designed to measure self-reflection more broadly than the Cyber Ball Task which is focused specifically on social self-esteem. As there is evidence that patient groups with high levels of negative self-evaluation find it hard to feel assured when performing cognitive and behavioural tasks (Lee, 2005), the FIQT should be able to pick up group differences in tendency to be self-critical, perfectionistic, worry and ruminate about performance rather than only measuring a single aspect of self-reflection. An additional strength of the FIQT, compared to the Cyber Ball Task, is that self-reflection is measured independent of actual performance - all participants perform the same and participants receive no feedback or cues to task performance – and therefore only participants' internal perceptions of performance affect outcomes.

The computerised version of the FIQT was first piloted in a group of patients with anorexia nervosa, as excessive self-criticism is associated with the instigation and maintenance of disordered eating behaviours (Starrs, Dunkley, & Moroz, 2015) and self-critical attitudes have been found to predict the development of anorexia nervosa (Fennig et al., 2008). These pilot studies indicated higher levels of negative self-reflection on all three subscales of the FIQT: self-comparison (against others); self-satisfaction; and perception of performance (self-identification of number of correct answers given) (Corfield, 2014; Patrick et al., Under Submission). This task has yet to be validated in patients with affective disorders and the neural correlates of the task have yet to be explored despite the task's suitability for adaptation into an fMRI paradigm and clear rationale for exploration in MDD and anxiety disorders. Gaining a better understanding

of self-reflective attitudes using improved tasks could be beneficial for predicting and tailoring treatment (due to the association of these concepts with treatment response, see Chapter 1) and better understanding common and distinct symptoms in and between disorders. More generally, the validation of this novel tool could provide a useful counter to traditional measures of self-reflection due to known issues with global self-report questionnaires and existing neuroimaging paradigms.

4.1.1 Hypotheses & aims

In order to test the psychiatric validity of the FIQT, we conducted two studies in patients with MDD and comorbid anxiety: behaviourally and as an fMRI task. The aims were to improve understanding of the FIQT's three subscale aspects of self-reflective attitudes in pathological and non-pathological functioning, as well as examination of the concepts tapped by the FIQT through exploring correlations with previously validated global self-reflection measures.

4.1.1.1 Behavioural sample

Higher scores in the patient group relative to controls were expected on all three subscales of the FIQT (self-disapproval, negative comparison with others, and perception of failure) due to the observed relationship between these factors and depression and anxiety (Dunkley et al., 2006; Zuroff et al., 2004). Positive correlations were expected between existing self-reflection measures and the FIQT, suggesting these tools approach similar aspects of self-reflection. To assess whether exposure to the FIQT incites changes in reported self-reflection over time, comparison of outcomes across trial blocks was conducted, with the expectation of no observable differences. To assess whether differences in task measures might be explained by differences in the perceived

importance of the task between groups, participants' post-task ratings of importance were compared in patients and controls with the expectation of no significant differences between groups.

4.1.1.2 Behavioural Results with therapy

A subset of participants completed the task twice - both before and after a course of CBT. It was expected that patients would have lower FIQT scores post- compared to pre-therapy due to CBT challenging negative self-reflective cognitions and evidence that psychological therapies reduce negative self-reflection (Rector et al., 2000). Additionally, it was predicted that treatment responders would show a greater reduction in FIQT subscale scores than non-responders as research has shown that the degree to which self-criticism reduces during treatment is a significant predictor of treatment outcomes for depression and social phobia (Blatt et al., 1995; Marshall et al., 2008; Rector et al., 2000). We also hypothesised that these patterns of reduction post-therapy would be found in self-report measures of self-reflection.

It was expected, due to evidence that those with higher levels of negative self-referential thought (including increased perfectionism, self-criticism and rumination) have poorer therapeutic responsiveness, that treatment responders would have lower baseline self-report scores (on the FIQT subscales and self-report self-reflection measures) than non-responders to CBT (Ciesla & Roberts, 2002; Egan et al., 2011; Jones et al., 2008; Mennin & Fresco, 2013; Schmaling et al., 2002; Shahar et al., 2004).

4.1.1.3 Neuroimaging sample

It was hypothesised that BOLD activity in DMN regions, in particular the PCC and mPFC which are considered crucial for the generation of self-reflective cognitions (Andrews-Hanna et al., 2010; Perkins et al., 2015), would be related to the task. Specifically, we

hypothesised that activation in the mPFC and PCC would be increased in the task's self-reflection versus the control condition. Additionally, this elevation would be greater in patients versus controls.

Due to evidence of differences in neural activation in self-reflective tasks versus resting-state scans (Whitfield-Gabrieli et al., 2011), we additionally expected, in addition to higher activation in DMN regions which is found in both resting-state scans and tasks based on self-reflection, that this task would invoke activation in brain regions involved in error processing. When individuals believe that they have made errors, have particular faults or undesirable attributes that could lead to social disapproval, this can be perceived as being a threat to the self (Gilbert & Irons, 2005; Rockliff et al., 2008). This internal focus on personal faults via error processing is relevant to the FIQT as we ask participants to evaluate their performance. We therefore expected to find brain activation in regions found to be crucially involved in error processing: the lateral PFC including the dorsolateral PFC (dlPFC) and dorsal ACC (dACC) (Garavan et al., 2003; Gehring & Knight, 2000; Longe et al., 2010). Additionally, the insula has been proposed to be involved in self-related processing (Modinos et al., 2009). Therefore, in addition to DMN regions, we expect to find elevated activation in these error processing regions and the insula in self-reflection versus control conditions and predicted that activation in these regions would be significantly greater in patients versus controls.

Additionally, we examined whether the neural activations observed were correlated with scores on self-report measures of self-reflection using multiple regression analyses. We hypothesised that elevated mPFC, PCC, ACC, insula and dlPFC activation would be positively correlated with FIQT subscale scores as well as self-report self-criticism, rumination, and worry and negatively correlated with self-reassurance scores.

4.2 Methods

4.2.1 The Fake IQ Task

The software for the FIQT, a computerised and adapted version of the "Impressions of Success and Failure Task" by Nuttin & Greenwald (1968), was programmed at the Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London.

Participants read a brief statement before beginning the task (see Appendix 3 for the full text) which informed subjects that the task was an examination of their visual perception and purposefully designed to be challenging and test their analytical ability. This statement was intended to increase participant expectation that the task is linked to intellectual ability and performance on which they would be judged, and minimise their expectation that self-reflective attitudes were in fact the measurements of interest. The explanation was consistent across participants to reduce any potential confounds arising from instruction interpretation. Participants were instructed to make quick and accurate judgements about predefined properties of two images of geometric shapes displayed side by side. This visual perception performance on the task was not measured; all problems were impossible in that the two geometric shapes are equivalent in terms of the criteria the participant had to judge them on, for example, length, surface area, or volume (see Figure 4-a). Individuals were debriefed after taking part in their follow up visit, and the necessary deception of the task explained.

The images were displayed, and the participant had 5.5 seconds to respond within. After a set of 10 images, participants were asked three questions about their perception of their performance to which they had 6.5 seconds to respond on a visual analogue scale (VAS) by holding down the left or right buttons/arrows to move the pointer with responses

ranging from 0-100. The pointer of the VAS was set to appear at a randomised start position varying from 30-70. This sequence, which included an average inter-stimulus interval between trials of 4.2 seconds, was repeated four times giving a total of 40 trials and a task length of 11 minutes, 17 seconds. All participants were given a practice session to familiarise them with trial timings and the response mechanism. The three questions were:

1) ***"How many of the last 10 trials do you think you got correct?"*** Answers from 'none' (0) to 'all' (100)
2) ***"Do you think your performance was better or worse than average?"*** Answers from 'much worse' (0) to 'much better' (100)
3) **"*Overall, do you feel satisfied with your performance*?"** Answers from 'very unsatisfied' (0) to 'very satisfied' (100)

Scores on these three questions were reverse scored so higher scores reflect more negative self-reflection (the questions had been presented in a more 'positive' framing to minimise causing a negative bias). These questions produce three subscale scores, as follows: 1) The number of estimated correct responses is reversed to give the number of estimated incorrect responses (**Incorrect** subscale), 2) the degree of positive self/other comparison becomes negative comparison to peers (**Comparison** subscale) and 3) satisfaction is translated in to level of dissatisfaction (**Dissatisfaction** subscale).

Additionally, after completing the task, participants were asked two questions:

1) To generally express how they felt during the task (this was used to determine whether they realised it was 'fake' and impossible).
2) "*Is how you performed on this task important to you?*" Answers from 'Not at all' (0) to 'Very Important' (10).

Differences between fMRI and behavioural task

In the event-related fMRI task (See Figure 4-a for example stimuli), after each set of images, the participant saw a screen saying either 'Wait' or 'Satisfied' displayed for 5 seconds with an inter-stimulus interval varying between 2-6 seconds afterwards (average of 4.2 seconds, a white cross presented on a black screen). On the 'Satisfied' trials, participants were instructed to reflect on their perceived performance on that trial (self-reflection trial). On the 'Wait' trials, the participants were instructed to not think about their performance but rather rest, relax and try to free their mind from the task (neutral/control trial). In the behavioural version of the task, after each image pairing the participant was asked "How satisfied were you with your performance" and had to respond on a VAS ranging from 0-100.

The participants' scores on the questions about their performance were used as measures of self-reflection and the neural activity on the 'Wait' (control condition) compared to 'Satisfied' (self-reflection condition) trials in the fMRI paradigm used as comparisons for neural activity relating to self-reflection.

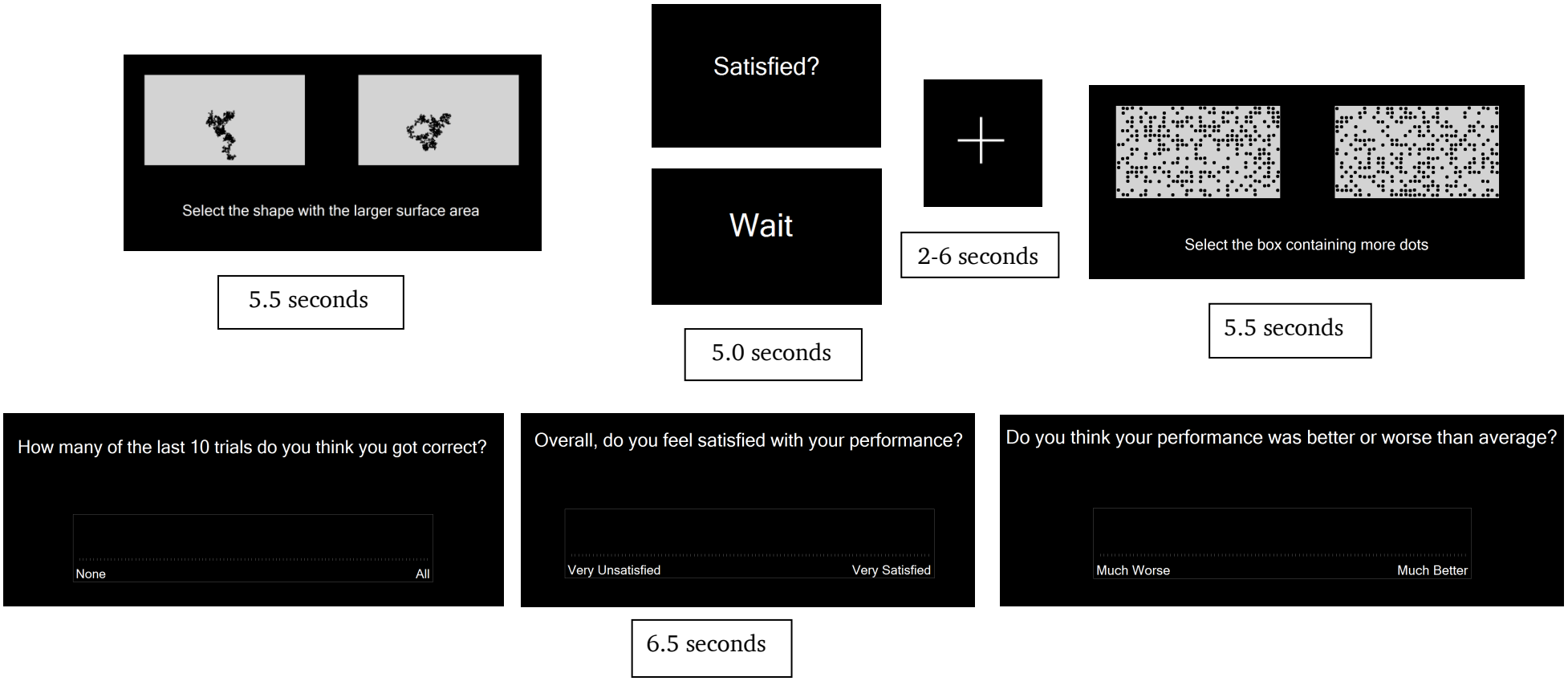


Figure 4-a: Example stimuli and display of the Fake IQ fMRI paradigm

4.2.2 Self-report questionnaires

Participants completed the following measures to allow examination of the association between the FIQT and existing self-report measures of self-reflection:

The Rumination Response Scale (RRS), a 22-item measure of rumination, self-reflection and brooding, where item scores are summed to give a total (Treynor et al., 2003). Questions, for example "Think about a recent situation wishing it had gone better" are rated on a 4-point scale from 1 ("almost never") to 4 ("almost always").

The Forms of Self Criticising/Attacking and Self-Reassuring Scale (FSCSR) (Gilbert et al., 2004). This is a 22-item questionnaire, with answers rated on a 5-point Likert scale ranging from 0 ("not at all like me") to 4 ("extremely like me"), exploring ways in which people respond when things go wrong i.e. one's tendency to be self-critical or self-reassuring to personal setbacks and failures. Two subscales measure different aspects of self-criticism, but can be combined to study overall self-criticism (e.g. as done by Gilbert et al., 2004). Additionally, there is a subscale capturing self-reassuring thoughts (total of 8 items, e.g. "I still like being me"). This questionnaire has been found to be a reliable measure with good psychometric properties (Baião, Gilbert, McEwan, & Carvalho, 2015).

The Penn State Worry Questionnaire (PSWQ), a 16-item questionnaire measuring trait worry (Meyer et al., 1990).

4.2.3 Behavioural statistical analysis

Differences in group performance were assessed with independent-samples t-tests. Effects between the FIQT and other measures of self-reflection (RRS, FSCSR, PSWQ) and depression severity (HDRS-17) were assessed with Pearson's correlations using False Discovery Rate (FDR) correction (Benjamini & Hochberg, 1995). A repeated-measures ANOVA was used to check whether first and final trial scores differed in the primary sample, which would be indicative of practice effects including participant's realising the 'fake' nature of the task.

Repeated-measures ANOVAs with Greenhouse-Geisser correction were conducted to test whether patient scores on self-reflection measures (FIQT subscales, PSWQ, RRS and FSCSR-SC) differed pre- to post-CBT. This was conducted in all patients undergoing therapy and additionally with treatment response as a between-subjects' factor. Independent samples t-tests comparing responders versus non-responders on all self-reflection measures (the FIQT subscales, RRS, PSWQ, and FSCSR-SC scales) were conducted on baseline and post-treatment data.

4.2.4 Neuroimaging analysis

4.2.4.1 MRI Acquisition

The functional MRI sequence comprised T2*-weighted gradient echo planar image (EPI) sessions of 338 whole brain volume acquisitions: flip angle 75°; TR = 2000 ms; TE = 30 ms; FOV = 24 x 24 cm; slice-thickness = 3 mm; inter-slice gap = 0.3 mm (total of 41 slices); matrix size = 64 X 64 voxels with an isotropic 3 mm x 3 mm in-plane resolution. A high-resolution T1-weighted image was also acquired as outlined in Chapter 3.

4.2.4.2 fMRI pre-processing

Pre-processing of data was conducted using custom Nipype scripts (http://nipy.org/nipype/), using tools from Statistical Parametric Mapping, Version 12 (SPM12, Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm/), and custom code. Functional images were realigned, slice time corrected, and co-registered to the high-resolution T1 image. T1 images were segmented and normalised and functional images were normalised into MNI space using deformation fields. Data were then smoothed using a 6mm full-width half maximum (FWHM) Gaussian kernel. To limit the effect of motion artefacts, participants with substantial translation of more than one voxel were removed from further analysis. Additionally, volumes with high levels of motion (based on realignment parameters and signal intensity changes from volume to volume) were identified using ArtifactDetect (implemented on Nipype) to be later removed from analysis. Physiological signals were processed using custom script implementing AFNI's RETROspective Image COrrection tool (RETROICOR) algorithm (Glover et al., 2000). This produced cardiac and respiratory regressors for use in first level analyses.

4.2.4.3 First and Second Level Analysis

Data were analysed using SPM12. First level models were formed on each participant's data to generate mean images for each participant that included regressors for each trial type ('Wait' (neutral condition), 'Satisfied' (self-reflection condition) and baseline fixation)), along with 6 motion parameters which were generated during realignment, and the physiological regressors generated by RETROICOR. In addition, motion scrubbing regressors were included to exclude volumes with high motion. This procedure has been shown to increase statistical power of fMRI analyses and reduce the impact of motion artefacts (Siegel et al., 2014).

The contrast of interest for our main effects analyses was formed by comparing the 'Wait' versus 'Satisfied' trials (controlling for fixation which was modelled as an implicit baseline condition). We tested for group effects between these conditions (differences in neural activation between patients versus controls) using one-sample t-tests in SPM12, with head motion (total distance travelled), age and sex as covariates.

We performed exploratory whole brain analyses due to this being the first use of this task. A cluster-defining threshold of $p < .001$ and a cluster-wise threshold of $p < .05$ FDR corrected for multiple comparisons was used across the whole brain.

In addition to whole brain analyses, we used an ROI approach. ROIs were derived from Neurosynth maps (neurosynth.org) for the term 'self-referential', thresholded at z>10 to identify regions most likely to be associated with self-reflective thought. This map was combined with the Automated Anatomical Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002) to create the ROIs and additionally eliminate non-DMN regions from these maps. Regions within default mode systems, especially the mPFC and PCC were selected due to these regions being considered imperative to the generation of self-referential thoughts (Perkins et al., 2015). The ROI analyses were conducted separately for each mask with a small volume correction. For these bidirectional ROIs, the significance level for the F contrasts were set to $p < .05$.

Regressions were conducted to explore relationships between neural activation on the task ('satisfied' compared to 'wait' conditions) and self-report measures of self-reflection. These included: the FIQT's subscale scores, self-criticism (FSCSR-SC), self-reassurance (FSCSR-RS), rumination (RRS), and worry (PSWQ) questionnaire scores. These regressions were conducted at both a whole brain level and on a mask of the main effect of the task (i.e. running correlations only in the areas that were significantly activated in the task) to explore correlations between behavioural scores and neuronal activity.

4.3 Results

4.3.1 Behavioural results

Thirty patients from both Study 1 and Study 2 (21 females, aged 35.2+-13.1 years) and 20 healthy controls (13 female, 32.0+-10.1 years) completed the FIQT behaviourally.

Significant differences were observed between the patient and control group on all measures (see Table 4-a). As expected, patients scored significantly higher on the HDRS-17, PSWQ and RRS measures and also scored significantly higher on the self-criticism subscale of the FSCSR scale, whilst scoring significantly lower on the self-reassurance FSCSR subscale. The patient group also scored significantly higher on all three subscales of the FIQT compared to healthy controls: the patients estimated that they made more mistakes (Incorrect, p <.05, d = .82, CI = 6.03 – 21.19, effect size – Cohen's d 0.81), gave greater ratings of perceived negative performance compared to peers (Comparison, p <.005, d = .90, CI = 5.4156 - 20.62, effect size – Cohen's d 0.90), and showed overall higher dissatisfaction (Dissatisfaction, p <.05, d = .61, CI = 1.67 – 19.27, effect size – Cohen's d 0.61). There was no significant difference between patients and controls in the post-task rating of importance they gave to performing well on the task.

Table 4-a: Descriptive statistics and independent samples t-test results for self-reflection measures, split by group.

	Patients Mean (SD)	Controls Mean (SD)	t
FIQT-Incorrect	54.1 (21.1)	40.6 (10.3)	2.7*
FIQT-Comparison	56.9 (18.5)	43.9 (8.5)	2.9**
FIQT-Dissatisfaction	54.4 (22.3)	43.2 (12.8)	2.0*
FIQT Importance	6.6 (2.4)	5.4 (2.8)	1.6
FSCSR – RS	12.5 (6.0)	25.6 (3.4)	-8.8**
FSCSR – SC	36.6 (4.0)	13.1 (7.9)	9.1**
HDRS-17	19.4 (4.0)	0.95 (1.4)	19.8**
RRS	66.8 (9.9)	31.4 (7.5)	13.6**
PSWQ	65.9 (7.5)	34.8 (11.8)	11.3**

Patients n = 30, Controls n = 20, * significant at $p < .05$, ** significant at $p < .001$.
Abbreviations - SD: Standard Deviation; FIQT: Fake IQ test; FSCSRS: Forms of Self-Criticising and Self-Reassuring Scale; SC, Self-Criticism; RS: Reassure Self; RRS: Ruminative Response Scale; PSWQ: Penn State Worry Questionnaire; HDRS-17: Hamilton Depression Rating Scale – 17 item.

Bivariate correlational analysis was conducted to explore relationships within the FIQT and between the FIQT, FSCSR, PSWQ, RSS and HDRS-17 (Table 4-b). Significant positive correlations were observed within both groups, between all subscales of the FIQT. However, no significant correlations were found between the FIQT subscales and self-report self-reflection or depression severity measures in either group.

No significant differences were found between the first and final trial in any of the FIQT subscales by group ($f(1) = .532$, $p = .469$), suggesting participant ratings did not change over time.

Table 4-b: Correlations between Fake IQ test subscales, the FSCSR, HDRS-17, RRS and PSWQ, by group.

Variable	1	2	3	4	5	6	7	8
1 FIQT-Incorrect	-	.87**	.76**	-.01	-.33	-.16	.28	.01
2 FIQT -Comparison	.94**	-	.82**	.11	-.35	-.18	.25	.01
3 FIQT –Dissatisfaction	.81**	.88**	-	-.28	-.16	.02	.01	-.14
4 FSCSRS-RS	.03	.01	-.13	-	-.51*	-.07	-.27	-.37
5 FSCSRS-SC	.19	.24	.26	-.65**	-	.37	.68**	.73**
6 HDRS-17	-.04	.08	.12	-.35	.29	-	.47*	.07
7 RRS	.11	.10	.10	-.26	.40*	.25	-	.64**
8 PSWQ	-.08	-.11	.00	.09	.29	.06	.11	-

N = 50 (correlations for 30 patients in lower half of matrix, 20 controls in upper half). * p <.05 level ** p <=.01. ***Abbreviations - FIQT: Fake IQ test; FSCSRS: Forms of Self-Criticising and Self-Reassuring Scale; SC: self-criticism; RS: Reassure Self; RRS: Ruminative Response Scale; PSWQ: Penn State Worry Questionnaire; HDRS-17: Hamilton Depression Rating Scale.***

4.3.2 Behavioural results with therapy

15 patients (9 females) with MDD and comorbid anxiety disorders completed the FIQT before and after a course of CBT (mean age 37.7+-15.2 years). The mean number of sessions of CBT attended was 10.3 (+-2.8), range 6-16 sessions. See Table 4-c for sample characteristics of both responders and non-responders to CBT. Responders were significantly younger on average than non-responders. Unexpectedly, non-responders did not have higher FIQT subscale, worry (PSWQ) or rumination (RRS) scores at baseline or post-therapy compared to responders. However, responders did have significantly lower self-criticism self-report scores (FSCSR-SC) post-therapy compared to non-responders as expected (p =0.02), but did not differ at baseline on this measure.

Table 4-c: Sample characteristics, split by treatment response

	Responders (n=6)	Non-responders (n=9)	Group Comparison
Age, years	26.3 (6.2)	45.3 (14.7)	t = 3.0*
Male/Female (n)	2/4	4/5	χ^2 = 0.2
Baseline MÅDRS	29.8 (7.7)	28.4 (7.0)	t = -0.4
Number of CBT sessions	8.7 (2.8)	11.4 (2.3)	t = 2.1
Baseline FIQT Incorrect	60.0 (19.5)	48.0 (29.7)	t = -0.9
Baseline FIQT Comparison	61.1 (20.5)	52.5 (22.8)	t = -0.7
Baseline FIQT – Dissatisfaction	64.2 (19.6)	44.5 (23.2)	t = 0.6
Baseline FSCSR-SC	41.2 (8.6)	36.4 (7.7)	t = -1.1
Baseline PSWQ	69.2 (6.8) †	63.3 (8.7)	t = -1.3
Baseline RRS	69.4 (5.9) †	66.8 (13.9)	t = 0.5
Post therapy FIQT Incorrect	58.0 (22.9)	38.5 (14.8)	t = -2.0
Post therapy FIQT Comparison	57.5 (15.1)	44.7 (14.6)	t = -1.6
Post therapy FIQT – Dissatisfaction	52.3 (15.2)	38.9 (17.1)	t = -1.5
Post therapy FSCSR-SC	20.7 (7.3)	33.2 (9.7)	t = 2.7*
Post therapy PSWQ	53.7 (13.4)	58.9 (9.4)	t = 0.9
Post therapy RRS	51.0 (13.4)	57.4 (12.3)	t = 1.0

†n=5 due to missing data for one participant. Values are reported as mean (standard deviation) unless otherwise stated. Comparison was by independent samples t-tests or Pearson chi-square for categorical variables. * Significant to *p* <.05. *Abbreviations - FIQT: Fake IQ test; MÅDRS: Montgomery-Åsberg Depression Rating Scale: CBT; Cognitive Behavioural Therapy; FSCSRS: Forms of Self-Criticising and Self-Reassuring Scale; SC: Self-Criticism total scale; RRS: Ruminative Response Scale; PSWQ: Penn State Worry Questionnaire.*

A repeated measures ANOVA on all patients (both responders and non-responders to CBT) showed no significant differences pre- to post-therapy on any of the FIQT measures: Incorrect ($f(1,14) = 1.16$, $p = .30$); Comparison ($f(1,14) = 2.79$, $p = .12$); or Dissatisfaction ($f(1, 14) = 2.26$, $p = .16$). There were significant differences though on all self-report measures of self-reflection from baseline to post-therapy: self-criticism (FSCSR-SC, $f(1,14) = 11.8$, $p = .004$), rumination (RRS, $f(1, 13) = 13.3$, $p = .003$), and

worry (PSWQ, f(1,13) =12.7, p = .003), all demonstrating reductions at time-point 2 compared to time-point 1.

Including treatment response as a between-subjects factor in the repeated-measures ANOVAs showed there were no significant group by time interactions on the FIQT subscales: Incorrect (f(1,13) = .36, p =.56); Comparison (f(1,13) = .25, p =.63); or Dissatisfaction (f(1, 13) = .38 , p =.55). With the self-report measures, there was no significant group by time interactions on the RRS: f(1,12) = 1.15, p =.31. However, significant effects were found on self-report self-criticism measured using the FSCSR-SC scale (f(1,13) = 18.65, p =.001) and worry measured using the PSWQ (f(1,12) = 5.54, p =.036). On both of these measures, treatment responders showed a greater reduction post-therapy compared to non-responders. These patterns of results were not altered when age was added in as a covariate to the repeated measures analysis due to significant differences between responders and non-responders in age.

4.3.3 fMRI results

Eighteen patients and twenty healthy controls completed the FIQT as an fMRI paradigm. However, three participants (two patients and one healthy control) were excluded from analyses due to excessive head motion during the task. Table 4-d shows participant characteristics for those included in these analyses. Patients scored significantly higher than the healthy controls on the RRS, FSCSR-SC, PSWQ and MÅDRS and significantly lower on the FSCSR-SR. Additionally, as with the behavioural sample, the patients scored significantly higher on the three subscales of the FIQT (Incorrect: p <0.5, effect size – Cohen's d 1.06; Comparison: p <0.5, effect size – Cohen's d 0.91; Dissatisfaction: p <0.5, effect size – Cohen's d 0.64).

Table 4-d: Sample characteristics of the Fake IQ test fMRI sample.

	Major Depression n = 16	Healthy control n=19	Group Comparison
Age, years	32.5 (11.5)	32.2 (10.2)	t = 0.2
Male/Female (n)	6/10	7/12	χ^2 = .42
MÅDRS	31.3 (6.5)	1.6 (2.0)	t = 17.2**
FSCSR - SC	33.7 (9.5)	12.7 (7.9)	t = 7.3**
FSCSR-RS	13.5 (5.6)	25.6 (3.5)	t = -8.1**
RRS	67.6 (7.7)	30.6 (6.7)	t = 13.8**
PSWQ	66.9 (7.5)	33.8 (11.3)	t = 9.7**
FIQT Incorrect	53.7 (14.6) †	40.2 (10.5)	t = 3.4*
FIQT Comparison	54.7 (14.7) †	43.7 (8.6)	t=3.1*
FIQT Dissatisfaction	53.4 (18.7) †	43.0 (13.1)	t = 2.3*

†n=15 due to data collection errors for one participant. Values are reported as mean (SD) unless otherwise stated. Comparison was by independent samples t-tests or chi-square for categorical variables. * *Significant to p <.05, ***** **Significant to *p* <.001.** ***Abbreviations - FIQT: Fake IQ test; FSCSRS: Forms of Self-Criticising and Self-Reassuring Scale; SC, Self-Criticism subscale; RS: Reassure Self subscale; RRS: Ruminative Response Scale; PSWQ: Penn State Worry Questionnaire; MÅDRS: Montgomery-Åsberg Depression Rating Scale.***

See Table 4-e and Figure 4-b for task main effects in both patients and controls. All results in the table met the criteria for significance: a cluster defining significance of $p < .001$ and a cluster-wise threshold of $p < .05$ FDR corrected. The tables include the significance level of the peak voxel within each cluster. There was increased activation if the self-reflection versus control condition bilaterally in the inferior cortex extending to dACC and insula, as well as left dlPFC, and motor area activation. There were no significant areas of decreased activation with self-reflection.

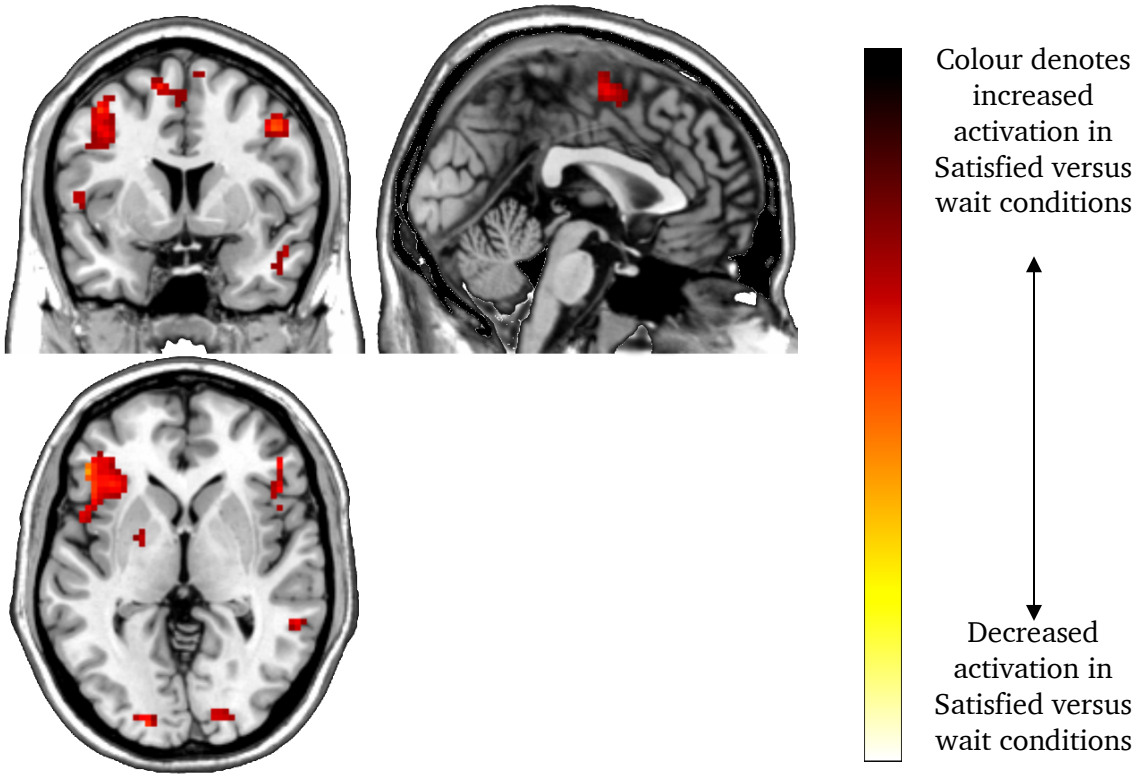
Table 4-e: Fake IQ Test Brain Activation (main effect of task)

Brain regions	Peak MNI co-ordinate	*P of peak cluster*	Voxels	F	Direction of activation
Left inferior occipital / left mid occipital cortex	-15, -91, -7	0.006	89	63.43	Satisfied>Wait condition
Left inferior frontal gyrus / dorsolateral prefrontal cortex / insula	-48, 32, -1	<0.001	486	38.62	Satisfied>Wait condition
Left inferior parietal cortex	-51, -49, 47	0.01	76	29.22	Satisfied>Wait condition
Right frontal inferior gyrus, slightly into right insula	51, 26, 5	0.006	90	27.85	Satisfied>Wait condition
Left supplementary motor area / left frontal superior cortex	-12, 5, 62	0.006	92	25.91	Satisfied>Wait condition

N = 35 (Patients = 16; Controls = 19), whole brain analysis. ***Abbreviations – MNI, Montreal Neurological Institute.***

No significant results were found in our ROI analysis. There was no significant difference in head motion between the groups (p =.55). No group effects (whole brain or ROI) showing significant differences in brain activation between patients compared to controls on the task were found. For the regression analyses, one patient was removed due to an incomplete dataset. No significant results were found whole brain or when the main effect of task was compared with other measures: the FIQT subscale scores or self-report measures of self-reflection (PSWQ, RRS and FSCSR-SC and RS).

Figure 4-b: Fake IQ test brain activation (Satisfied > Control conditions)



4.4 Discussion

This chapter presents a psychiatric validation of the FIQT, an objective measure of self-reflection based on the "Impressions of Success and Failure" experiments by Nuttin & Greenwald (1968). As hypothesised, the patient group scored higher than the healthy participants on all FIQT subscales, indicative of lower levels of implicit positive self-evaluation. No association was found between task measures and treatment response perhaps suggesting the domains measured with the FIQT are more indicate of trait, rather than state, self-evaluation. BOLD response on this novel task (comparing active self-reflection versus control trials) in patients and controls was also examined. A main effect of task was found with greater activation in the self-reflection versus the control condition

bilaterally in the inferior frontal cortex, insula, motor cortex and dACC. However, no group differences in neural activation, or correlations with FIQT subscale scores or self-report measures of self-reflection were found.

4.4.1 Discussion of results from the behavioural task

The patient group showed significant differences compared to the control group in all three subscales of the task: heightened negative comparison to others, higher self-dissatisfaction, and greater perceived failures. These findings were expected due to evidence of high self-criticism, low self-esteem and heightened perception of failure in depression (Beck, 1967; Blatt, 2004; Dunkley & Grilo, 2007; Nuttin & Greenwald, 1968) and anxiety disorders (Blatt, 2004; Dunkley & Grilo, 2007).

No relationship was found between scores on pre-existing self-reflection scales (the FSCRS, RRS, or PSWQ) and the FIQT, despite scores on all measures being significantly raised in the patient group. As such, data do not support the notion that the FIQT is a direct alternative to current self-report measures. Self-report questionnaires of self-reflection use broad, global statements, which relate to general experience without context (e.g. “I find it difficult to control my anger and frustration at myself” (Gilbert et al., 2004) or “Think about how passive and unmotivated you feel” (Nolen-Hoeksema et al., 2008)). Comparatively, the FIQT assesses perception of performance in a specific context. Considering the role of self-report bias which may be particularly problematic in a self-critical and ruminative sample (Offer et al., 2000), it is informative how contextual restriction in assessment (and without any feedback) can tease out differences in self-reflection. Many researchers have challenged the idea of a single-concept and instead favour a multidimensional approach to self-critical attitudes (Castilho, Pinto-Gouveia, & Duarte, 2015). The FIQT and current self-report measures may be tapping differential

concepts of self-reflection, together contributing to a more comprehensive picture of pathological self-judgement.

Additionally, no correlation was observed between depression severity and the FIQT, contrary to our hypothesis. It may be that the sample size was too small to reveal detailed differences related to symptom severity, despite our results indicating sensitivity to pathology. As the MDD sample included patients with co-morbid anxiety, it may also be that anxiety-based symptomology and clinical heterogeneity was affecting this relationship.

The FIQT subscales showed strong internal correlation, suggesting that dissatisfaction with task performance, number of estimated incorrect responses, and negative comparison with peers are related. Importantly, comparing scores on the FIQT subscales across blocks indicates that the task does not appear to have induced negative self-appraisal, which would have been shown in increasingly negative scores on the measures over time, in either the patient sample or healthy controls. Additionally, the false nature of the task did not appear to have been picked up quantitatively, which could have been demonstrated by increasing or decreasing levels of task satisfaction over the blocks if the participant had guessed they were completing an impossible task and altered responses accordingly. Indeed, self-report from the participants (after completing the task and being unblinded as to its fake nature) showed that no participant fully guessed that there were no quantifiable differences between the shapes (although a few of the participants had mild suspicion the task was unsolvable and when they were informed that it was fake after the second application were not shocked). The task was therefore successful in its ability to deceive.

There was no significant difference between patients and controls in the post-task rating of importance they gave to performing well on the task which adds credibility that

differences between groups are not due to healthy controls caring less about performance but are reflective of differences in self-perception of performance. Additionally, mean scores of 6.6 and 5.5 in patients and controls respectively suggest that subjects viewed their performance as being relatively important which suggests that self-esteem could be impacted and measured in task performance subscales. However, it should be noted that the scale characteristics of importance (rated on a scale of 0-10) may have made this measure less sensitive than a VAS of 0-100, as used for the subscale scores on the Fake IQ test. This may have potentially obscured any difference between patients and controls and therefore this finding should be interpreted cautiously. Patients did indeed score just over one point higher on rated importance which is translated to a 0-100 VAS scale could have led to finding significantly different ratings between groups. Future use of the task should ensure consistent scales are used across all task-related measures.

4.4.1.1 Sensitivity of the FIQT to treatment response

We hypothesised that patients would have significantly lower FIQT subscale scores post- compared to pre-therapy due to evidence that CBT reduces negative self-referential processing (Rector et al., 2000). Further to this, we postulated that responders would show a greater reduction in FIQT scores than non-responders. We did not find this pattern of results as there were no significant differences in FIQT scores over time nor an interaction between time point and treatment response. We also hypothesised that these patterns of reduction post-therapy would be found in self-report measures of self-reflection (the RRS, FSCSR-SC, and PSWQ). Indeed, we did find that patients scored significantly higher pre-treatment compared to post-treatment on all self-report measures. It was also found that this decrease in scores was significantly greater in responders than non-responders in self-report self-criticism (FSCSR-SC) and state worry (PSWQ).

These results may suggest that self-report questionnaires measure more state aspects of self-criticism than the FIQT, which could be argued to reflect trait-related aspects of self-referential processing. Alternatively, the questionnaire measures could be more sensitive to change, illustrating patient's subjective experiences of a reduction in their levels of self-criticism, worry and rumination in everyday life. These experiential reductions may not translate to how they actually behave in certain situations (for example, the Fake IQ test) with these behavioural changes taking longer to emerge or requiring a longer course of therapy to alter. Due to evidence showing that negative self-referential thoughts are not only associated with poorer treatment response but also a more fragile response trajectory (i.e. these patients have a higher risk of relapse) (Jones et al., 2008; Mennin & Fresco, 2013), it could be that our follow up was too short to reveal any group differences on the FIQT. Alternatively, the FIQT could measure an aspect of self-referential behaviour that is not relevant to treatment response in depression and anxiety. To determine whether the FIQT is sensitive to treatment response, further investigation is warranted. Studies should explore this in larger samples, with a longer follow up and in alternate samples, for example, those who have remitted or are at risk of developing depression/anxiety. This could help elucidate how much of a trait or state measure of self-reflection the FIQT is.

Due to our finding that FIQT subscale scores did not correlate with existing self-report measures of self-criticism, rumination and worry, further work should explore the FIQTs relationship to alternative negative self-reflective processes for example self-report self-blame (Marschall et al., 1994), perfectionism (Frost et al., 1990) and self-punitiveness (Carver & Ganellen, 1983). The latter of which is proposed to consist of three components including: 1) perfectionism in setting high, possibly unattainable standards; 2) negative, self-critical responses to failures and setbacks; and 3) overgeneralisation to

disappointments, each of which can be measured using the Attitudes Towards Self Scale (Carver & Ganellen, 1983) to determine which, if any, component is related to FIQT scores. The FIQT may more closely measure these aspects of negative self-reflection which have been argued to be personality trait measures and therefore may be less amendable to change (Blatt et al., 1995) explaining why the observed changes in self-report self-criticism, rumination and worry with treatment were not observed in FIQT scoring.

It was expected, due to evidence that those with higher levels of negative self-referential thoughts have poorer therapeutic responsiveness, that treatment responders would have lower baseline self-report scores (on the FIQT and self-report measures) than non-responders to CBT (Ciesla & Roberts, 2002; Egan et al., 2011; Jones et al., 2008; Mennin & Fresco, 2013; Schmaling et al., 2002; Shahar et al., 2004). This was not found on any measure except for self-report self-criticism (FSCSR-SC) post-therapy where responders scored significantly lower than non-responders. It is likely that the sample size of this pilot study was too small to reveal any group differences should they exist.

4.4.1.2 Strengths of the use of the FIQT as a behavioural task and suggested future work

The FIQT may measure additional dimensions of self-criticism that are not covered by traditional self-report questionnaires. It is suitable for use in multiple experimental paradigms, including drug and neuroimaging studies. Importantly, comparing scores on the FIQT subscales across blocks indicates that the task does not appear to have incited negative self-appraisal, an issue with studies using valance feedback (Besser et al., 2004).

The work presented in this thesis complements pilot studies that also tested this measure (albeit with slight methodological differences in response scoring mechanisms) in patients with anorexia nervosa (Corfield, 2014; Patrick et al., Under Submission). These studies also found patients to score significantly higher on all three FIQT subscales versus

matched healthy controls and therefore the psychiatric validity of this task has now been replicated in two patient groups. Future work should explore this task in alternate disorders, in particular those associated with reduced self-reflection, such as autism spectrum disorders or psychopathy (Philippi & Koenigs, 2014). The minimal use of vocabulary and removal of global introspection on the FIQT means this measure is applicable to groups with special requirements (for example, young children). Additionally, previous work has suggested self-criticism may mediate between maladaptive perfectionism and psychological distress (James et al., 2015); future work could evaluate the role of this factor alongside the FIQT in psychopathology.

4.4.1.3 Weaknesses of the use of the FIQT as a behavioural task

The patient sample was not selected to exclude co-morbid anxiety disorders; it would be beneficial to explore FIQT output in both MDD and anxiety disorders separately controlling for co-morbidity which could be affecting the resulting pattern of results. Although this was an exploratory investigation to pilot this novel task, we appreciate that the sample sizes are relatively small.

This work focuses on quantitative differences in self-evaluation but there may be important qualitative differences as well such as distinctions in the quality or content of self-reflective thoughts between groups. In depression, we typically think of negative ruminative thoughts about the self, e.g., I am worthless / inadequate / to blame. In GAD, worries are often about potential threats to the self, health problems, or worries about one's future. Subsequent studies could explore qualitative differences in thoughts surrounding the FIQT which may reveal important differences across disorders, an understudied area in this field (Philippi & Koenigs, 2014).

Regarding our null finding of changes in task measures with therapy and in relation to treatment response, this may demonstrate that the task measures more ingrained trait aspects, rather than state characteristics, of self-evaluation. Indeed, there is evidence that the ability to be self-reassuring and resilient when things go wrong is a result of early attachment style and temperament (Masten, 2001; Mikulincer & Shaver, 2007) and therefore there may be aspects of self-reflection that are less amenable to change. Specialist therapy, focusing on self-compassion and reassurance, may be more likely to result in changes in this behaviour (Gilbert & Irons, 2005) despite evidence showing that CBT does reduce negative self-reflection by challenging negative cognitions (Beck, 1970; Mennin & Fresco, 2013; Rector et al., 2000). Future work should explore the task in relation to different forms of therapy, especially those specifically targeted to negative self-reflective processes. Longer term follow-up, in order to understand any long-term association with treatment outcome, as well as administering the task to remitted or at-risk populations could elucidate the task's sensitivity to treatment response.

4.4.2 Discussion of neuroimaging results

We hypothesised that the self-reflection versus control condition of the FIQT would be associated with higher activation in DMN regions (predominantly the mPFC and PCC), the insula, dlPFC, and dACC. We found evidence of increased insula, dACC and dlPFC activation in line with our predictions and literature associating these regions with self-reflective tasks of error processing (Garavan et al., 2003; Gehring & Knight, 2000; Longe et al., 2010; Modinos et al., 2009). Additionally, significantly elevated activation in the self-reflection condition was found in the posterior inferior parietal lobe. This region is part of the DMN and associated with attending to visual, spatial stimuli (Zhang & Li,

2014); however, no further DMN activation was found against our expectation due to this network being considered crucial for self-reflective cognition (Philippi & Koenigs, 2014). The observed elevation in activation in inferior, occipital and parietal cortices could be interpreted, along with the raised dACC and insula activation, in terms of the increased emotional salience of the self-reflection trials. These regions form part of the 'salience network' which is associated with the processing of salient, internally-generated emotional thoughts (Uddin, 2015). The insula is thought to mediate the detection of motivationally salient and emotional stimuli (Paulus & Stein, 2010) and the 'salience network' has been found to have reciprocal connections and causally influence activity in the DMN (Uddin, 2015). Our finding of elevated motor activation in the self-reflection condition could be due to the participants imagining the shapes and translating them mentally. Indeed, motor imagery has been found to mimic the brain activity found during actual motor movement (Miller et al., 2010).

Not finding elevated mPFC and PCC activation in the self-reflection condition, two key DMN regions thought to be essential for the generation of self-reflective cognition, could be due to the design of the task in that the control condition still somewhat comprises a self-reflection condition. Resting-state studies, where participants often report being engaged in self-reflective thought, find involvement of the DMN and the FIQT's control condition is similar to resting-state scans where the participant is instructed to rest. This could additionally explain why our ROI analyses did not reveal any significant task effects, due to our focus on DMN regions in selection of these regions. Despite evidence of differences between resting-state and task-based self-reflective neural activation, many studies do use similar control conditions to ours in self-reflective tasks and find DMN activation (Whitfield-Gabrieli et al., 2011). Perhaps our small sample size limited our ability to find such an effect.

We expected to find increased activation in all brain regions associated with the task in patients versus controls due to our expectation that patients would be engaged in elevated levels of self-reflection. However, no group differences in neural activation were found. Larger sample sizes are required to determine the sensitivity of this neuroimaging task to psychopathology. Additionally, no correlations with BOLD response and self-report measures of self-reflection were found. This backs up our findings from behavioural piloting of this task where we found no significant associations between FIQT scores and self-report rumination (RRS), self-criticism (FSCSR) or worry (PSWQ). Future studies should consider the relationship of the FIQT with alternate measures of self-reflection to determine if the FIQT more closely reflects, for example, self-blame or perfectionist aspects of self-reflection. There remains the possibility that the task, having been designed to have no emotional content or performance feedback, is simply an assessment of a general negative bias in perception of abilities rather than a robust measure of self-reflection more generally.

Regressions were also conducted on FIQT subscale scores and neural activation but no associations were found. This prevents us from interpreting whether the regions of increased activation on the self-reflection compared to the control condition relate to negative or positive forms of self-reflection. For example, elevated insula activation has been associated with increased self-reassurance and compassion (Farb et al., 2007; Longe et al., 2010; Lutz et al., 2008) but we are not able to confidently interpret such a direction from our findings. The FIQT is designed to measure the whole spectrum of self-reflective thoughts; for example, individuals may engage in high levels of self-reassurance or exhibit reduced self-reflection which the task has been designed to measure alongside negative cognitions. Future research is required to determine associations between neural activation on the FIQT and self-report measures. As self-reflection is considered as a

spectrum, with both high and low levels found in a range of psychopathologies, a better understanding of the neural correlates of specific aspects of self-reflection may inform us about the development and maintenance of disordered thinking.

4.4.2.1 Strengths of the FIQT as an fMRI paradigm

To date, no studies to our knowledge have explored the neurophysiology of implicit self-reflection. One of the key benefits of this task in its potential as a neuroimaging paradigm is that it is a more implicit measure of self-reflection than existing tasks. Self-reflective neuroimaging paradigms often require the individual to recall or envisage a self-critical attitude and therefore rely on the assumption that internally imagined states are equivalent to those produced by external means, which has been questioned in the literature (Klein & Gangi, 2010; Prigatano & Fordyce, 1986). The FIQT has the advantage of avoiding invoking imagination when assessing self-reflective cognitions as the task creates the state. Additionally, the task is suitable for a wide range of patient populations due to its minimal use of vocabulary and removal of global introspection; for example, it is appropriate for young children.

In this pilot study of the FIQT as an fMRI paradigm we were able to demonstrate a main effect of task. Potentially due to our limited sample size, we did not find significant differences in neural activation between patients and controls, or an association between brain activation on the task and self-report measures. Further research is required in larger sample sizes to further validate the task as well as determine what aspects of self-reflection the FIQT is tapping into by looking at associations with other measures of self-reflective cognition.

4.4.2.2 fMRI limitations and suggested refinements to the FIQT

A potential reason for not finding significant differences between patients and controls on the task (self-reflection versus control condition) could be that the patient group were not able to shift their attention to this 'wait' or relaxation condition i.e. they could not inhibit self-reflective thought and shift their attention away from negative self-evaluation within the timescales necessitated by the fMRI paradigm. Alternatively, patients may have had higher activation (i.e. engaged in higher levels of self-reflection) in both conditions. Both of these may have confounded group differences. Indeed, some participants reported that the 'Wait' and 'Satisfied' conditions felt too short to fully reflect on their satisfaction or relax. Further work should determine if the length of the self-reflective and control conditions impacts results. Additionally, patients may not have been able to relax and free their mind due to self-compassion being an inaccessible emotion to patients, who have been found to respond with threat like responses when they are asked to be self-soothing (Rockliff et al., 2008). This, along with the design of the task whereby the control condition still somewhat reflects an inherently self-reflective condition, may have compounded our ability to detect group differences.

Future studies could pilot the task with alternative control conditions or analyse the self-reflection condition against baseline (when participants fixated on a blank screen with a cross between trials). Alternate control conditions could include a distractor (for example, hand-tapping, or thought cues such as thinking about the shape of Africa or the layout of a local supermarket) which may minimise self-reflective cognitions (Johnson et al., 2006; Nolen-Hoeksema & Morrow, 1993; Roelofs et al., 2009). However, our control condition was designed so as to match the self-reflection condition as closely as possible to control for confounds, such as differences in displayed visual information, motor and external cognitive stimulation. Potentially suitable distractor tasks could be cues for the

participants to reflect on the properties of the presented shapes in the task – for example asking the participants to think about what the images looked like or trying to memorise their properties. This is external and not internal self-reflection and could be cued with a single word (as with the self-reflection condition), for example 'shape'.

Our lack of significant differences between patients and controls may be interpreted as indicating that neurally the task is not sensitive to pathology. However, we believe further exploration is warranted as other studies have found differences in patient groups associated with negative self-reflection and further, self-reflective tasks have been shown to be sensitive to therapeutic response, for example, with pharmacological (Kilts et al., 2006) and psychological therapies (Yoshimura et al., 2014). Our relatively small sample size in this piloting of the task may have hindered us from detecting significant differences should they exist.

4.4.3 Overall conclusion

One promising method of approaching the need to develop more pathophysiologically-based systems of diagnosis and predictors of response in psychiatry (Insel et al., 2010) is to identify quantitatively measurable, specific dysfunctions in cognitive or behavioural domains that are related to distinct pathology (Hyman, 2007). This research has initiated exploration of a task that has been designed with various advantages over existing measures and could contribute to this goal. The presented data suggests the task is sensitive to clinical pathology and gives an interesting insight into the role of self-dissatisfaction, negative performance evaluation and self-depreciation in depression and anxiety. The FIQT appears to tap aspects of self-reflection not accessible to existing self-report questionnaires and has strong potential for use in a wide range of patient populations and study design. We did not find that the FIQT was sensitive to treatment

response nor find differences in neural activation during the task between patients and controls. Despite this, we believe further work should be conducted in the task both in relation to treatment response and in relation to brain activity, and associations with alternative measures of self-reflection. Small sample sizes may have hindered our ability to detect effects should they exist. Further research is therefore required before strong conclusions can be drawn, due to the novelty of the FIQT, as well as our sample size.

Chapter 5: Dynamic functional connectivity in the default mode network in major depression: a two-sample validation study[2]

Chapter summary

Altered static, or average, functional connectivity strength over the course of a resting-state scan has been found in various brain networks in major depression. These functional abnormalities have been suggested to reflect the negative thinking styles characteristic of the disorder, particularly in the default mode network (DMN), which is associated with self-referential thought. Dynamic functional connectivity, the study of temporal fluctuations in connectivity strength, is a relatively novel analysis technique which has not been applied widely in affective disorders to date despite the method's potential to inform us in greater detail about connectivity abnormalities.

We assessed the stability of connectivity between two key nodes in the DMN associated with negative self-reflection: the medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC). This functional connectivity stability was assessed over the course of a multi-echo resting-state magnetic resonance imaging scan and compared between Study 1 patients (n=19) and healthy controls (n=19). The replicability of results was assessed in an independent sample using a standard, single-echo resting-state scan. The validation sample was a group of patients with un-medicated unipolar depression (but free from

[2] This chapter has been adapted from the following publication on which I am joint first author: Wise, T. and Marwood, L et al. (2017). Instability of default mode network connectivity in major depression: a two-sample confirmation study. *Translational Psychiatry, 7*(4), e1105. DOI: 10.1038/tp.2017.40.

other psychiatric comorbidities). All patients (n=20) were right-handed and their respective control group (n=19) matched for age, handedness and sex.

Significantly greater variability in connectivity between the mPFC and PCC was identified in the patient group in both samples, suggesting that the results were reliable and not due to the fMRI resting-state acquisition approach used or due to the specific patient group recruited. These results demonstrate that aberrant connectivity in the DMN in depression goes beyond alterations in connectivity strength and suggest that individuals with major depression show increased variability in functional connectivity within this key functional circuit. Replicating the results in two independent samples is a specific strength of this work suggesting that the findings are robust.

These outcomes add a further dimension to theories that suggest altered functional connectivity underlies some of the symptoms of mood disorders and may be associated with rumination. Further research is required to understand the nature of these fluctuations in this newly emerging field of research and to understand their relationship to the aetiology of depression, anxiety and rumination.

5.1 Introduction

In major depression, alterations have been identified within both structural and functional brain networks (Kaiser 2015; Wise et al., 2015). One of the most studied networks is the DMN, which has been proposed to underlie self-referential thought including negative rumination (Andrews-Hanna et al., 2010; Perkins et al., 2015). A recent meta-analysis of static functional connectivity studies in major depression found hyper-connectivity within the DMN and fronto-parietal systems (Kaiser, Andrews-Hanna, et al., 2015). In particular, the subsystem of the DMN connecting the medial prefrontal cortex (mPFC) with the posterior cingulate cortex (PCC) is considered crucial in generating affective, self-directed thoughts as outlined in the introductory chapter of this thesis (Andrews-Hanna et al., 2010; Perkins et al., 2015).

Recent work in functional connectivity has begun to look beyond average, or static, connectivity and develop a richer understanding of the dynamic nature of these networks by examining how their connectivity changes over time, so called dynamic functional connectivity (Calhoun et al., 2014; Hutchison et al., 2013; Kopell et al., 2014). To date, few studies have been published using this method (Calhoun et al., 2014; Hutchison et al., 2013) with one study in major depression (Kaiser, Whitfield-Gabrieli, et al., 2015). This study found increased variability in connections between the mPFC and insula and decreased variability between the mPFC and parahippocampal gyrus in a large sample of patients with depression (n=100) (Kaiser, Whitfield-Gabrieli, et al., 2015), suggesting that alterations in dynamic functional connectivity are present in MDD. Despite the mPFC and PCC being considered crucial in the generation of negative self-reflective thoughts, Kaiser et al. 2015 found no significant differences in variability between these regions, potentially due to the whole-brain analysis method used in their analysis, which may have lacked power to identify an effect.

5.1.1 Aims and hypotheses

In this study we aim to further understand mPFC dynamic interactions with the PCC in depression given their relevance to negative self-referential cognitions associated with affective disorders (Andrews-Hanna et al., 2010; Perkins et al., 2015). To investigate the dynamic nature of interactions within this network, we examined the variability of connectivity between these two regions in participants from Study 1. We then evaluated the robustness of our results by seeking replication in an independently recruited sample with similar characteristics. Additionally, we tested the association of measures of self-reflection and depression severity with dynamic functional connectivity between these regions.

Kaiser et al. found increased connectivity variability between the mPFC and insula in patients with major depression versus healthy controls. Although not strictly part of the DMN, this part of the 'salience network' has been found to reciprocally influence the DMN when processing salient, internally–generated, emotional thoughts (Uddin, 2015), and activation in these regions has also been found to correlate with level of rumination (Kaiser, Whitfield-Gabrieli, et al., 2015). Due to these findings, we hypothesised increased connectivity variability in patients with major depression versus healthy controls between the mPFC and PCC and hypothesised that this variability would be correlated with self-report measures of self-reflection.

We tested these hypotheses in two samples of medication-free patients with major depression: Sample A (participants from Study 1) and Sample B (an independent validation sample who were selected to be free from psychiatric comorbidity). These two separate samples were selected to validate the robustness of results arising from the study

which is encouraged in fMRI (Nichols et al., 2017). As the two samples varied in their presence of clinical comorbidities, this allowed the stability of the result with clinical heterogeneity to be tested. Additionally, the fMRI acquisition parameters varied between samples – multi-echo versus standard single-echo fMRI pulse sequences in Samples A and B respectively. This allowed us to test that results were not due to non-neural artefacts owing to utilising the recently developed multi-echo fMRI which is superior to traditional de-noising methods of extracting BOLD signal from non-BOLD signal components of resting-state data (Kundu et al., 2012).

5.2 Methods

5.2.1 Participants

Sample A

Sample A comprised patients and healthy controls from Study 1 (see Chapter 3 of this thesis for full details of inclusion and exclusion criteria).

Sample B

Sample B included patients and healthy controls from the validation sample detailed in Chapter 3 of this thesis.

5.2.2 Functional MRI acquisition

Data were acquired on the same model of scanner for each sample - identical GE MR750 3 Tesla scanners with 12-channel radiofrequency head coils. The same high-resolution T1-weighted structural scans were acquired in both studies (TR = 7.31ms, TE = 3.02ms, 256 x 256 matrix, 196 slices, voxel size = 1.2 x 1.05 x 1.05mm). For the resting-state

scans, data were acquired in the following sequences: Sample A, an 8-minute multi-echo sequence (TR = 2300ms, TEs = 12.7/31/48ms, FOV = 24cm, flip angle=90˚, 33 slices, resolution = 3.75 x 3.75 x 4.2mm) and; in Sample B, a 6-minute single-echo resting-state scan was acquired using a T2*-weighted echo-planar imaging sequence (TR = 2000, TE = 30ms, FOV = 22.1cm, flip angle=75°, 39 slices, resolution = $3.3mm^3$). In both studies, participants were instructed to keep their eyes open and fixate on a cross displayed on a computer screen for the duration of the resting-state scan. Cardiac and respiratory signals were recorded throughout the duration of the scans. Sample B was an opportunistic, validation sample and therefore the scanning parameters differed from Sample A.

5.2.3 Functional MRI pre-processing

Pre-processing of data was conducted using Nipype scripts (http://nipy.org/nipype/) using tools from SPM-12, the FMRIB Software Library (FSL 5.0.9, http://fsl.fmrib.ox.ac.uk/), and Analysis of Functional NeuroImages (AFNI, https://afni.nimh.nih.gov/afni/), along with custom code created by Dr Toby Wise.

The four first volumes of the resting-state series were deleted to allow the magnetisation to reach equilibrium, before slice-timing correction was applied and the images were realigned and co-registered to the T1 structural images. For Sample B, cardiac and respiratory physiological signals were regressed from the data using AFNI's RETROspective Image CORrection tool: RETROICOR (Glover et al., 2000). For Sample A, multi-echo data were pre-processed using the multi-echo independent component analysis (ICA) tool in AFNI (Kundu et al., 2012) to isolate components in the signal likely representing true BOLD signal. This was used in place of RETROICOR for the multi-echo data as it has been shown to be a more effective method of de-noising multi-echo data (Kundu et al., 2012). Except for the method outlined above for de-noising the data, which

varied due to the method of image acquisition, all proceeding processing steps were identical for both samples to ensure comparability between the two data sets.

Data were next demeaned, de-trended, and smoothed with a 6mm FWHM Gaussian kernel. Further pre-processing included correction for six rigid-body movement parameters (three translations and three rotations, which were determined from the middle echo image for Sample A) and extracting time series from white matter and CSF regions along with regressing these signals from the data. Data were high-pass (0.008 Hz) and low-pass (0.09 Hz) temporally filtered to remove low frequency signal drifts and high-frequency noise in the data.

5.2.4 Head motion

Time points in the data with substantial motion were identified in the BOLD time series as even small head movements can affect signal and correlations in resting-state data if not controlled for (Power et al., 2012). We assessed motion at each time point using the FSL motion outliers tool with its default thresholds using root mean square (RMS) intensity difference between volumes and DVARS (Derivative of rms VARiance over voxelS, which is a measure of how much the intensity of a brain image changes from one volume to the next) (Power et al., 2012). Instead of removing time points exhibiting excessive motion, data were inserted at these points using 3rd order b-spline interpolation. This was so as not to affect the length of the sliding window in the dynamic functional connectivity analysis, and hence dynamic connectivity estimates. All analyses were conducted on the pre-processed and motion scrubbed data.

Motion was compared between the samples in terms of total distance travelled, framewise displacement (head movement from one volume to the next) and absolute displacement (movement of the head from the origin position at each time point) (Power et al., 2012).

5.2.5 Definition of regions of interest

Canonical ICA, a data driven method, was used to identify DMN components in the data (Varoquaux et al., 2010). This was implemented in Nilearn (machine learning for Neuroimaging in Python, https://nilearn.github.io/) using 20 clusters. Clusters centred on the PCC and mPFC regions in the identified DMN component were used to create regions of interest (ROIs) for the connectivity variability analysis. This process was conducted separately for the two samples to identify more accurate, sample-specific ROIs as anatomy and connectivity can vary considerably between individuals and therefore defining the ROI for one sample and applying it to the other sample could lead to inaccuracies (Poldrack, 2007). The size of each ROI was set to a sphere of 10mm diameter, centred on the peak of each cluster from the canonical ICA analysis. Limiting the size of the ROI, instead of using the whole cluster, ensured a more consistent signal, less affected by activation in surrounding regions.

We also extracted a negative control region to ensure that any results relating to these ROIs were specific to these regions rather than being a global brain-wide pattern or caused by non-neural influences. The negative control ROI, not previously linked to depression, was a 10mm spherical region in the medial primary motor cortex (MNI co-ordinates: -1, -8, 63). Mean time series were extracted from each of these ROIs.

5.2.6 Sliding window correlation analysis

Most studies of dynamic functional connectivity have used a sliding window approach to investigate the changes in correlations across the course of a scan (Allen et al., 2012; Kiviniemi et al., 2011). This method involves conducting connectivity analyses on a set number of scans in an fMRI session (a defined window) and then repeating the analysis shifting the window by a certain number of scans.

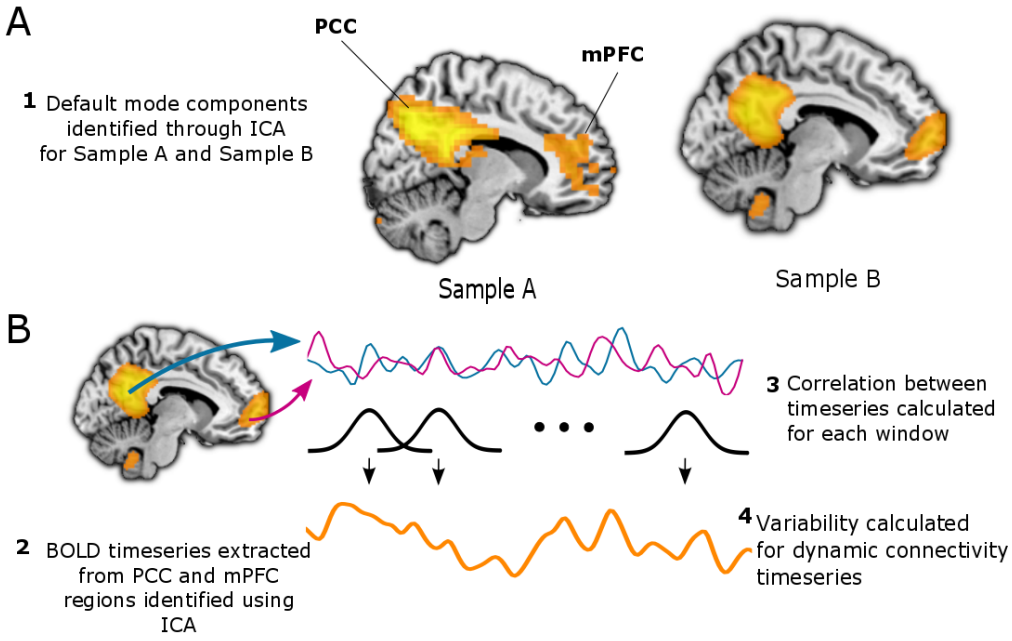
Our sliding window analysis was conducted using custom Python scripts created by Dr Toby Wise (https://www.python.org/). The window was set at 40-seconds and staggered by one TR. We used a Gaussian window, which produces a tapered window (see Figure 5-a for an illustration of the analysis technique). It has been shown that window lengths of greater than 30 seconds are sufficient to measure robust effects (Shirer et al., 2011). The time period we chose has been shown to be appropriate for dynamic functional connectivity analysis previously, providing a detailed depiction of temporal connectivity changes (Zalesky & Breakspear, 2015). While longer windows are suitable for investigating low-frequency changes in connectivity strength, they fail to detect higher frequency fluctuations, as illustrated via simulation data in the supplementary material of the published version of this chapter (Wise et al., 2017). The simulation data validated the method used here and showed that we are likely measuring real and not spurious fluctuations in connectivity based on our choice of window length and high-pass cut-off frequency.

Within each window, the correlation between variance-normalised time series were calculated from the two ROIs using Pearson correlations. These results were transformed to Z-scores. The standard deviation of these correlations was calculated, giving a measure of variability of these correlations. Any participant with outlying variability, defined as greater than three standard deviations from the mean, were removed from further analyses.

The relationship between connectivity variability and clinical measures was explored using Pearson partial correlations in both samples: depression (total MÅDRS score) and anxiety severity scores (HDRS-17 anxiety subscale e.g. (McClintock et al., 2011), time since illness onset (years) and self-report level of rumination (measured using the total score on the RRS,(Treynor et al., 2003). In Sample A, additional correlations between

connectivity variability were conducted with self-report measures of worry (total score on the PSWQ, (Meyer et al., 1990) and self-criticism (measured using a total of the two self-criticism subscales of the FSCSR scale, Gilbert et al., 2004).

Figure 5-a: Dynamic functional connectivity method.



A) Image of the default mode network components identified using ICA, showing clusters in the mPFC and PCC (step 1). B) Illustration of the dynamic functional connectivity sliding window analysis method (steps 2:4). *Abbreviations - PCC: Posterior cingulate cortex, mPFC: Medial prefrontal cortex, ICA: Independent Component Analysis.*

5.2.7 Static functional connectivity analysis

To understand any relationship arising between static and dynamic functional connectivity, we calculated static functional connectivity between the ROIs. This was

conducted by calculating the average connectivity strength between these regions using the whole, non-windowed time series.

5.2.8 Voxel-based morphometry analysis

Additionally, we examined the existence of grey matter volumetric differences in the chosen ROIs and at a whole-brain level between patients and controls which could account for any differences found in connectivity. The high-resolution T1-weighted structural images were pre-processed using voxel-based morphometry in SPM-12 and the images segmented into different tissue types using DARTEL (Ashburner, 2007). Images were then normalised in MNI space. The grey matter images were smoothed with an 8mm FWHM Gaussian kernel before the grey matter volume was compared in the mPFC and PCC ROIs between patients and healthy controls with a two samples t-test. An uncorrected voxel-wise threshold of $p < .001$ was used, with a cluster threshold of $p < 0.05$, FDR corrected. A whole brain comparison, looking at total grey matter volume in the segmented maps between groups, was calculated at a threshold of $p < .05$.

5.2.9 Additional analyses

Additional statistical analyses were conducted using R (R Core Team, 2015). Group comparisons and correlations were corrected for the number of comparisons using FDR correction: mPFC-PCC, PCC-negative control region, and mPFC-negative control region. Additionally, group comparisons and correlations were adjusted for total head movement (distance travelled), age and sex of the participant.

5.3 Results

5.3.1 Participants

Nineteen patients with unipolar major depression in Sample A and twenty patients in Sample B were matched with 20 and 19 healthy controls in each sample respectively (see Table 5-a for participant characteristics). A healthy participant from Sample A was excluded from the analyses due to outlying variability values.

The two samples did not differ in terms of depression severity (total MÅDRS scores): $t(37) = -1.83$, $p = 0.07$. However, as expected due to the higher levels of comorbid anxiety disorder in Sample A, this sample had significantly higher anxiety scores: $t(37) = 3.45$, $p = 0.001$. Sample A also had significantly higher RRS scores: $t(37) = 3.51$, $p = 0.001$ and a longer illness duration (time since illness onset): $t(37) = 2.62$, $p = 0.01$ than Sample B.

The peak MNI co-ordinates of the ROIs in each sample were identified in Sample A as: mPFC: 2, 60, -4; PCC: 6, -44, 11 and in Sample B: mPFC: 4, 60, 0; PCC: 2, -62, 22.

Table 5-a: Sample Characteristics

	Patient Groups	Control Groups	*p*
Sample A			
Age, years	32.34 (10.62)	31.91 (10.30)	0.90
Male/Female (n)	7, 12	6, 13*	0.73
MÅDRS	30.74 (7.31)	1.37 (1.86)	< .001
HDRS anxiety subscale	7.16 (1.30)	0.31 (0.58)	< .001
RRS	66.47 (8.22)	30.63 (6.83)	< .001
FSCRS: SC scale	33.60 (9.84)	13.89 (9.68)	< .001
PSWQ	63.05 (11.45)	37.11 (14.98)	< .001
Time since illness onset (years)	13.50 (8.26)	-	-
Comorbid diagnoses	N=12 (9 GAD, 5 SAD, 4 OCD, 2 PD, 2 PTSD, 1 historic substance abuse)	-	-
Previous hospitalisations	4 participants	-	-
Number of depressive episodes	4 (2.5)	-	-
Sample B			
Age (years)	29.55 (6.59)	30.05 (6.71)	0.81
Male/Female (n)	2, 18	2, 18	1
MÅDRS	27.25 (4.24)	0.95 (1.39)	< .001
HDRS anxiety subscale	4.95 (2.48)	0.21 (0.42)	< .001
RRS	56 (10.23)	29.67 (6.44)	< .001
Time since illness onset (years)	6.35 (6.41)	-	-
Comorbid diagnoses	None	-	-
Previous hospitalisations	0 participants	-	-
Number of depressive episodes	1.5 (1.25)	-	-

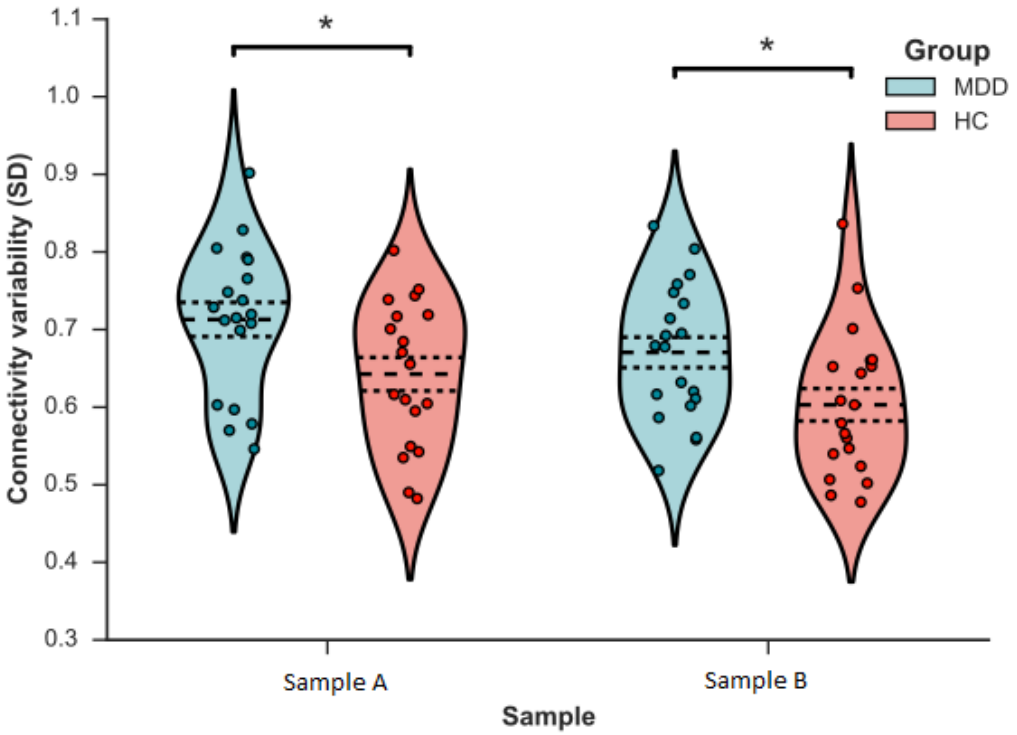
Demographics for Sample A represent the 19 healthy controls included in the final analysis. Values are reported as mean (standard deviation) apart from number of previous episodes where, due to skewed data, we instead report median (interquartile range).** ***Abbreviations - MÅDRS, Montgomery-Åsberg Depression Rating Scale: HDRS, Hamilton Depression Rating Scale (17 item): RRS, Ruminative Response Scale: FSCRS SC: Forms of Self-Criticising/Attacking and Self-Reassuring Scale: Self Criticism subscale: PSWQ, Penn State Worry Questionnaire: GAD, Generalized Anxiety Disorder: SAD, Social Anxiety Disorder: OCD, Obsessive Compulsive Disorder: PD, Panic Disorder (with or without agoraphobia): PTSD, Post-Traumatic Stress Disorder.

5.3.2 Connectivity variability

Connectivity variability (the standard deviation of connectivity strength) between the mPFC and the PCC over the course of the sliding windows (see Figure 5-b) was significantly greater in patients with major depression versus healthy controls in both Sample A ($t(36) = 2.53$, $p = .045$, $d = 0.82$) and Sample B ($t(37) = 2.56$, $p = .044$, $d = 0.82$). This replication across samples supports the consistency of this finding regardless of the method of image acquisition and presence of clinical heterogeneity in the patient groups.

In the negative control regions, there were no group differences in connectivity variability between the mPFC and primary motor cortex in either sample (Sample A: $t(36) = 1.85$, $p = .22$ or Sample B: $t(37) = 0.79$, $p = .44$), or between the PCC and primary motor cortex in either sample (Sample A: $t(36) = 0.63$, $p = .99$ or Sample B: $t(37) = 1.76$, $p = .17$). This suggests the results found in connectivity variability in the DMN do not represent global brain instability differences.

Figure 5-b: Connectivity variability between the mPFC and PCC for patient and healthy control groups in both samples.



Plots represent the distribution of data in each group, along with individual participant data points. Larger dashed lines represent means and small dashed lines, standard errors. ***Abbreviations - MDD: Major depressive disorder, HC: Healthy control, SD: Standard deviation; * p < .05 in comparison between patient and control groups.***

5.3.3 Static connectivity

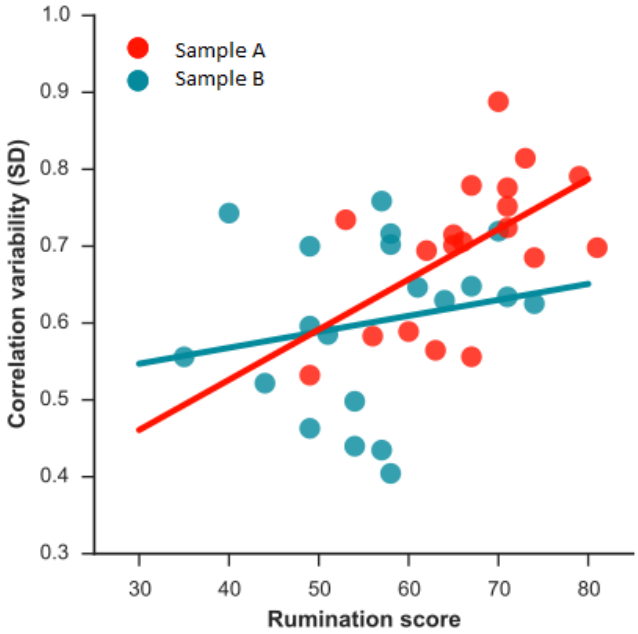
There was no significant difference between patients and healthy controls in static connectivity strength between the mPFC and PCC in either Sample A: $t(36) = .75$, $p = 0.45$, d = 0.24) or Sample B: $t(37) = 0.33$, $p = .74$, d = 0.11.

5.3.4 Connectivity variability and self-reflection measures

In the patient group in Sample A, a positive correlation between RRS and connectivity variability was found ($r(14) = 0.51$ $p = .045$, see Figure 5-c). This was not found in Sample B ($r(15) = 0.18$, $p = .48$). In Sample A, the additional correlations with other self-report measures of self-reflective thoughts were not found to significantly correlate with connectivity variability (worry: $r(14) = -0.04$, $p = 0.88$ or self-criticism: $r(14) = 0.21$, $p = 0.43$).

Figure 5-c: Correlation between connectivity variability and rumination (RRS score) in major depression in the both samples.

SD: Standard deviation.



5.3.5 Correlations with clinical variables

No significant correlations between connectivity variability and the following clinical variables were found in either sample: depression symptom severity (Sample A: $r(14) = 0.16$, $p = 0.56$, Sample B: $r(15) = 0.37$, $p = 0.14$); anxiety symptom scores, measured

by the anxiety subscale of the HDRS (Sample A $r(14) = -0.55$, $p = 0.56$, Sample B: $r(15) = 0.11$, $p = 0.66$); or time since illness onset (Sample A: $r(14) = 0.10$, $p = 0.71$, Sample B: $r(15) = 0.25$, $p = 0.33$).

5.3.6 Grey matter volumes

There was no significant difference in total grey matter volume between the patient and control groups (Sample A: $t(36) = 0.79$, $p = 0.43$ or Sample B: $t(37) = 1.43$, $p = 0.16$). Nor any differences between groups in grey matter volume in the selected ROIs (no significant clusters at $p < 0.05$, FDR corrected thresholds).

5.3.7 Head motion

A comparison of total head distance travelled between patients and controls showed no significant differences in either Sample A: $t(36) = 0.56$, $p = 0.58$ or Sample B: $t(37) = -1.31$, $p = 0.20$. Additionally, there were no significant differences between groups in mean framewise displacement (Sample A: $t(36) = 0.26$, $p = 0.80$, Sample B: $t(37) = 0.88$, $p = 0.38$) or maximum absolute displacement (Sample A: $t(36) = 1.48$, $p = 0.15$, Sample B: $t(37) = 0.42$, $p = 0.68$). Furthermore, there were no significant differences in the number of interpolated time-points in the fMRI series between groups in either Sample A: $t(36) = 1.60$, $p = 0.12$ or Sample B: $U(37) = 173$, $p = 0.64$ (non-parametric test used due to non-normally distributed data). This suggests group differences in connectivity variability are not attributable to motion.

5.4 Discussion

5.4.1 Interpretation of findings

We compared temporal variability in connectivity strength within the DMN between medication-free patients with major depression and healthy controls and found that connectivity between the mPFC and PCC, two key nodes of the DMN implicated in depression, was significantly more variable in the patient group. We replicated this finding in an independent sample free from comorbidities and using a different method of image acquisition, highlighting the robustness of our result.

The current findings complement previous research which has found abnormal dynamic connectivity in depression (Kaiser, Whitfield-Gabrieli, et al., 2015) and add to the growing field of dynamic functional connectivity research generally (Calhoun et al., 2014; Kopell et al., 2014). Despite the recent emergence of this field, a number of studies have begun to identify alterations in dynamic functional connectivity in other psychiatric conditions such as schizophrenia (Damaraju et al., 2014; Ma et al., 2014), Alzheimer's disease (Jones et al., 2012; Wee et al., 2015) and bipolar disorder (Rashid et al., 2014). These findings, along with the results of the present study, suggest that dynamic connectivity holds promise for providing a clearer, novel insight into connectivity abnormalities in psychiatric disorders.

The previous study assessing dynamic functional connectivity in unipolar depression by Kaiser et al., demonstrated altered connectivity variability between the mPFC and insula, and decreased variability in connectivity between the mPFC and parahippocampal gyrus in depression. They did not find any significant altered connectivity variability between the mPFC and PCC, the areas under investigation in this study. This lack of finding might

be explained by the more limited power in whole brain analyses used in Kaiser et al.'s study, due to the necessary correction for multiple comparisons.

Presently, the causes of time varying properties of connectivity are not well understood (Hutchison et al., 2013). One potential explanation for our findings is that they result from altered structural connectivity which has been associated with dynamic functional connectivity – higher structural connectivity being associated with more stable dynamic functional connectivity (Shen et al., 2015). Therefore, it is plausible that the increased connectivity variability between the mPFC and PCC we found was a result of reduced structural integrity. However, we believe this to be unlikely as a recent meta-analysis found that patients with depression do not have reduced integrity in the tracts connecting these regions (Wise et al., 2015). We therefore believe that these results reflect primary functional alterations as opposed to being secondary to aberrant structural connectivity. However, research clarifying the exact causes of connectivity variability, and its relationship to static connectivity is an important area for future research.

It is possible that the functional alteration found is related to negative self-reflection. The DMN, and mPFC-PCC connectivity in particular, is believed to underlie self-referential thought (Hamilton et al., 2011; Perkins et al., 2015). As a result, high levels of intrusive, self-generated, ruminative thoughts may be associated with fluctuations in connectivity within this network. In Sample A, we found a positive correlation between connectivity variability and trait rumination, which is in line with this explanation. This association with rumination, however, was not found in Sample B, and as such this finding should be interpreted with caution and warrants further investigation. It is possible that this may be due to differences in the clinical characteristics of the samples. For example, patients in Sample A had more comorbid anxiety disorders, higher average RRS scores, and had experienced a greater number of previous depressive episodes. However, we did not find

an association in Sample A between variability and self-report self-criticism and worry (two other measures of self-reflection) calling into question links with all forms of self-generated thought.

Despite not finding a consistent association with rumination, we cannot rule out that the heightened variability we found is not related to ruminative thought processes. We used a trait measure of rumination which may not reflect state levels of rumination experienced during the scans. A measure of reported rumination throughout the scan may be required. This also applies to our measures of self-critical thoughts and worry and could explain our null results. A post-scan report method was used in a previous study in healthy controls (Kucyi & Davis, 2014) which revealed a positive correlation between variability in the DMN and reported daydreaming, a related phenomenon to rumination, during scanning. This indicates that variability of connectivity within the DMN may be associated with daydreaming or self-reflection. Building on this, alterations in these processes might underlie the results with rumination shown here, although this merits confirmation in further work with post-scan measures of self-reflection during scanning or alternative global self-report measures of self-reflection (the limitations of current methods to assess self-reflection are discussed in Chapter 4).

It is possible that alterations in dynamic connectivity observed here reflect neuronal level processes. Simulation studies have indicated that patterns of synchronisation and de-synchronisation in neuronal populations lead to fluctuations in functional connectivity (Honey et al., 2007), while noise-driven neuronal simulations produce switches between states of functional connectivity (Hansen et al., 2015). A simultaneous electroencephalography (EEG) and fMRI study has shown that changes in BOLD functional connectivity coincide with EEG power variations (Tagliazucchi et al., 2012) further indicating that fluctuations in functional connectivity are reflective of neuronal

processes. Whether the observed increased connectivity variability in major depression is reflective of neural functioning corresponding to certain cognitive or emotional states or whether it is an abnormal neurophysiological function, perhaps causing increased noise in neural circuits, is not clear. Indeed, due to the lack of certainty surrounding the causes and correlates of variability in dynamic functional connectivity (Hutchison et al., 2013), we are limited to speculative interpretations about what they may imply in terms of pathological neural activity in depression.

No association was found in either sample between connectivity variability and depression severity which may suggest that variability is not directly related to depressive symptoms. Alternatively, our lack of association could be due to our measure of symptom severity, the MÅDRS, being heavily weighted to physical symptoms of depression rather than cognitive or psychological aspects. Indeed, previous research has suggested that alterations in DMN connectivity are more likely to be related to psychological symptoms such as negative self-referential thought patterns (Hamilton et al., 2011), which could explain our null results. In addition, studies have found symptoms to be uncorrelated with biological disease processes which is likely due to their unreliable nature and indirect relationship with biological mechanisms (Calhoun et al., 2014).

It has previously been suggested that static hyper-connectivity will imply lower temporal variability in connectivity (Chang & Glover, 2010; Kaiser, Whitfield-Gabrieli, et al., 2015); however, this is at odds with our results, where we did not find static hyper-connectivity between groups but did find increased temporal variability. Our results therefore suggest that the relationship between dynamic and static connectivity is complex with dynamic functional connectivity providing distinct information about network communication in pathology independent from, and beyond that of, static connectivity. This echoes findings from previous research (Calhoun et al., 2014; Rashid et al., 2014) that classified patients

with schizophrenia, bipolar disorder and healthy controls based on functional connectivity and found that classification using a combination of static and dynamic connectivity was more accurate than static connectivity alone. Our findings are concordant with this, in that they demonstrate that each form of connectivity provides distinct and complementary information.

5.4.2 Strengths and limitations

A key strength of this study is our control of non-neural influences on the data. It is well known that resting-state fMRI analyses are susceptible to influences from confounding factors such as subject motion and physiological variables, such as heart rate and respiration (Glover et al., 2000; Power et al., 2012); however, we thoroughly controlled for these. Firstly in Sample B, we corrected for cardiac and respiratory signals using the RETROICOR method (Glover et al., 2000) to limit the influence of physiological factors. Secondly, in addition to regressing out motion parameters, as is commonly done in fMRI analysis, we scrubbed time points exhibiting high motion in both samples. This technique has been shown to limit the occurrence of spurious correlations in resting-state connectivity analysis (Power et al., 2012). Finally in Sample A, we used multi-echo fMRI with ICA-based de-noising, which has been shown to be more effective than traditional de-noising methods at distinguishing true BOLD from non-BOLD signal (Kundu et al., 2013, 2012). Together, these measures ensured that effects of confounding factors on our results were limited, and we can be confident that our results do not simply reflect physiological or motion-related artifacts. Moreover, our negative control analyses (with a motor cortex ROI) indicated that our findings were not reflective of global differences between groups and were instead specific to the disease-relevant network. We also showed that the patient and control groups did not differ on motion parameters and therefore motion artefacts cannot explain group differences.

A further strength of the present study is that all patients were free from psychotropic medication at the time of scanning, and as such our results are not due to an acute effect of pharmacotherapy. In addition, many patients in Sample B were medication naïve and had experienced few, if any, depressive episodes previously, making it less likely that the effects observed here are cumulative effects of illness or previous therapies. The fact that altered connectivity variability was also found in Sample A, which included patients with more chronic and heterogeneous illnesses, suggests that variability may not be modified by extended illness or be specific to a distinct patient population. Additionally, the two samples resting-state data being acquired by different methods – single versus multi-echo image acquisition – further increased confidence in the findings not being due to methodological parameters. However, causality cannot be inferred from our results, and further research is necessary to replicate these outcomes and determine whether alterations in dynamic functional connectivity play a role in the aetiology of major depression. Furthermore, it is unclear from this study whether heightened variability in connectivity in key nodes of the DMN is specific to the depressed state or whether this is a trait marker of vulnerability to depression. Studies in remitted patients or in individuals at heightened risk of depression will be required to answer this question. Additionally, longitudinal studies scanning patients before and after psychological or pharmacological therapy could explore whether treatment normalises this increased variability.

A limitation of this study is the ROI approach used. We focused on two regions of the DMN, chosen due to their key role in affective disorders and negative self-reflective thoughts (Andrews-Hanna et al., 2010; Fransson & Marrelec, 2008; Perkins et al., 2015), and limited our analyses to these *a priori* regions of interest to increase our power to detect changes given our relatively small sample sizes. It would have been of interest to replicate the findings of Kaiser et al.'s, for example, altered variability in the insula.

However, we chose to focus on the key areas of the DMN that have been most linked to aberrant levels of self-reflection in affective disorders given the novelty of this field to reduce likelihood of type 2 errors given our small sample sizes. Despite the relatively small samples, the replication of the results across the two samples increases our confidence that the results are not spurious. We selected the ROIs separately for each sample using canonical ICA, a data driven method. Alternative and widely used methods for selecting ROIs in fMRI analysis are based upon brain atlases or previous functional studies. A group ICA approach is less affected by noise in the data and avoids prior spatial assumptions (Cole et al., 2010; Sohn et al., 2015). However, there is still the issue of defining the region of interest across all groups in a given study as the method of canonical ICA, takes into account but, does not fully control for individual variability. Canonical ICA has been shown to provide better group level data than other ROI selection approaches (Varoquaux et al., 2010). However, although the same ICA method was applied to both samples in this chapter, it cannot be fully ruled out that the regions identified do not align precisely in terms of anatomical regions between the groups.

A further limitation was the length of the resting-state imaging sequences. The multi-echo sequence for Sample A was only 8 minutes long, and in Sample B, only 6 minutes. Less frequent fluctuations in connectivity may therefore have been missed in these relatively short sequences. Due to high comorbidity between anxiety and depression, it is impossible to rule out the possibility that these results are reflective more of anxiety symptoms. However, as we found the same effect in separate samples, with differing levels of comorbid anxiety, this is unlikely. Further work is required to determine if the increased variability in connectivity found is common across all affective disorders or specific to depression.

5.4.3 Overall conclusion

In conclusion, our study shows that major depression is associated with increased variability in the DMN, which is likely to represent an intrinsic neural property of disease related, network-specific brain function that cannot be explained by structural abnormalities or static functional connectivity. A major strength of our study is that we could replicate the result in a second independent sample, suggesting that our finding is robust. More generally, this work highlights the importance of studying functional connectivity dynamically to gain a more detailed picture than previous static functional connectivity studies in this field. As ruminative thoughts may partially explain our results, further work is required to explore the link between self-referential thoughts *during* the scanning session and connectivity variability. Additionally, future work should investigate whether connectivity variability differences are specific to the depressed state, a vulnerability marker, or common to all affective disorders.

Chapter 6: Threat-related pursuit and goal-conflict in patients with depression and anxiety versus healthy controls

Chapter Summary

Threat avoidance is a prominent symptom of anxiety disorders and major depression, yet its biological basis remains poorly understood. In particular, it is unclear what neural systems underlie distinctions between anxiety and fear in pathological avoidance and anticipation of perceived threats. Here we used a validated task, the Joystick Operated Runway Task (JORT), involving avoidance of mild electric shocks, combined with fMRI, to explore whether abnormal function in circuits responsible for avoidance underlies these symptoms. Behavioural performance on this task was also studied in a comparison between patients with depression and comorbid anxiety disorders and healthy controls, and in relation to response to cognitive behavioural therapy due to this treatment targeting aberrant levels of avoidance and attentional bias towards threats.

Eighteen individuals with major depression and comorbid anxiety disorders, in addition to seventeen healthy controls, performed the in-scanner task which involved using physical effort to avoid threatening stimuli, paired with electric shocks on certain trials. Activity during anticipation and avoidance of threats was explored and compared between groups. Behaviourally, 29 participants (16 patients and 13 healthy controls) and 14 patients before and after a course of cognitive behavioural therapy completed the JORT.

Anticipation of avoidable aversive stimuli was associated with significant activation in the dorsal anterior cingulate cortex, superior frontal gyrus and striatum, while active avoidance of aversive stimuli was associated with activity in dorsal anterior cingulate cortex, insula and prefrontal cortex. No differences in neural activation were observed between healthy controls and patients. Behaviourally, there were no significant differences in JORT measures between patients and controls despite patients reporting to experience more dread whilst being chased on the task. Additionally, JORT behavioural measures did not significantly change post- compared to pre-therapy.

Our results suggest that the task was effective in identifying neural systems involved in avoidance and anticipation of aversive stimuli. However, the absence of significant differences in activation between patients and controls suggest that major depression is not associated with abnormal function in these networks. Similarly, no group differences were found behaviourally on the JORT task and performance was not found to be related to response to cognitive behavioural therapy. Future research should investigate the basis of passive avoidance in major depression and this task should be further explored in patients with anxiety disorders (free from comorbid major depression), where threat avoidance may be a more prominent characteristic of the disorder.

6.1 Introduction

As discussed in the introductory chapter (Chapter 1), threat sensitivity is a compelling model for explaining psychiatrically relevant individual differences in proneness to negative emotion owing to the capacity for drugs with clinical effectiveness against affective disorders to alter innate defensive reactions to threats (Blanchard et al., 1990;

Griebel et al., 1995; Perkins et al., 2013; Perkins et al., 2009) and this concept underlying many psychological therapies (LeDoux et al., 2017). Threat avoidance is proposed to comprise of two forms of defensive direction in Gray and McNaughton's reinforcement sensitivity theory: fear when escape is possible and anxiety where escape is not always possible and threats require approach (Gray & McNaughton, 2000). However, much of the evidence for this differentiation comes from rodent models of threat avoidance.

As such, these defensive directions had previously been studied in isolation of one another in humans until the development of the Joystick Operated Runway Task (JORT) by Dr Adam Perkins which allows within-task, within-subject comparison of these elements of threat behaviours. The JORT is an adaptation of the Mouse Defence Test Battery (MDTB, Griebel et al., 1997) which is an established active-avoidance model used to study threat behaviour in mice when they are chased by an anaesthetised rat under both simple pursuit (fear) and goal-conflict (anxiety) conditions. In the human translation of this task, participants are chased by digital predators on a computer screen under two equivalent active-avoidance conditions: pursuit trials when participants are chased by one predator requiring flight behaviour, and goal-conflict conditions when participants are chased by two predators which leads to an approach-avoidance conflict. The task requires the participant to engage in physical effort to avoid getting caught thus mimicking real-world threatening experiences. On certain trials the innately fearful threats are paired with mild electric shocks or loud bursts of aversive white noise, adding an additional element of threat by association with a cued aversive event. Along with anxiety and fear related behaviours, defensive intensity is another aspect of threat avoidance that can be measured on the task by quantifying the overall speed, acceleration and oscillations in movement made by participants to avoid getting caught (Perkins et al., 2009, 2011).

In support of the differentiation between fear and anxiety being psychiatrically relevant, Perkins et al. (2011) found that flight behaviour on the JORT was increased in healthy participants determined post-hoc to have a genetic risk factor for panic disorder, compared to participants without the risk factor. In addition to increased flight behaviour, carriers of the risk gene for panic disorder reported being more fear prone via self-report on the tissue damage fear subscale of the Fear Schedule Survey (Wolpe & Lang, 1964), but not more anxiety prone.

The task was also piloted behaviourally in healthy participants across two blinded, randomised, within-subject trials to explore the effects of the anti-anxiety drug lorazepam versus the anti-panic drug citalopram on defensive direction. It was found that lorazepam decreased Risk Assessment Intensity, a measure of anxiety on the task (i.e. the level of forward-backward oscillations during approach to threat) but that citalopram did not significantly decrease Flight Intensity on the pursuit trials as expected (a measure of fear related behaviour) (Perkins et al., 2009). A second study further exploring the effects of lorazepam on threat behaviours by Perkins et al. (2013) found a personality-dependent effect of lorazepam on Flight and Risk Assessment Intensity. Specifically, lorazepam was found to increase Risk Assessment Intensity in those with high trait anxiety scores but decrease it in low scorers. In contrast, lorazepam was found to decrease Flight Intensity on those scoring high on a measure of fear and increase Flight Intensity in low scorers.

Evidence from the JORT task is therefore mixed in terms of support for the reinforcement sensitivity theory, suggesting that the model, which is based largely on rodent studies, may be too simplistic or not translate precisely to human avoidance behaviours. Potentially, psychotropic medications may have broader modes of action in humans than rodents. Nevertheless, further work has supported the differentiation in humans via self-report questionnaire data which has shown specific associations between trait anxiety and

threat approach, and fear with orientation away from threats (Perkins & Corr, 2006; Perkins et al., 2007).

As the JORT's behavioural studies have shown that the task's goal–conflict and pursuit trials are differentially sensitive to anxiolytic medication, and potentially psychiatrically relevant measures, the JORT has been adapted to be suitable as an fMRI paradigm to facilitate understanding of the brain systems underlying fear and anxiety. Rodent studies have found that pursuit of threat activates midbrain regions and that goal-conflict is governed by the hippocampus (Gray & McNaughton, 2000). Ethological fMRI studies in humans, albeit in healthy controls and using other rodent paradigms such as foraging or maze based tasks with chasing virtual predators, provide evidence of similar brain systems governing threat-related pursuit and goal conflict. Prefrontal regions such as the ACC and ventromedial prefrontal cortex (vmPFC) and low-level midbrain regions (such as the PAG) have been found to be activated in threat pursuit (Mobbs et al., 2009, 2007), whereas the anterior hippocampi have been found to be activated in goal-conflict tasks (Abraham et al., 2013; Bach et al., 2014; O'Neil et al., 2015) as well as more recently the amygdala (Korn et al., 2017). Prefrontal cortices have been found to be activated with distal threats, possibly reflecting the higher level cognitive planning of threat-avoidance, whereas midbrain regions have found to be activated when threats are close, potentially reflecting a shift to evolutionarily older brain regions that control reflexive defensive behaviours such as flight, fight and freeze behaviours (Mobbs & Kim, 2015; Mobbs et al., 2007). These ventral midbrain regions have also been associated with basic reward and incentive motivation (Mobbs & Kim, 2015).

The fMRI version of the JORT was first piloted in healthy control participants (Perkins et al., Under Submission). In line with other human and rodent research, differentiations were found between pursuit and goal-conflict conditions with midbrain and prefrontal

activation being associated with flight in pursuit trials and hippocampal activation being associated with goal-conflict (Bach et al., 2014; Mobbs et al., 2009, 2007). The runway design of the task allowed the measurement of the effect of threat distance on brain activity; however, no main effect of the threat of receiving an electric shock was found. Perkins et al. also found that brain activation was associated with psychological measures. Lower hippocampal activation in goal-conflict plus imminent threat was associated with higher neuroticism scores, which suggests that those with a personality more susceptible to anxiety and depression have altered goal-conflict processing under threat. This adds further to evidence suggesting that affective disorders reflect alterations in the functioning of brain systems which govern responses to threat.

The JORT has thus far only been validated in healthy participants. Due to the potential psychiatric relevance of the task, observed association between neural activation on the JORT and neuroticism, and sensitivity to psychotropic medications behaviourally, we piloted the measure in patients with depression and comorbid anxiety disorders. Due to findings linking depression and anxiety disorders with elevated attentional focus on threats and negative anticipation (Grupe & Nitschke, 2013), we also evaluated brain activation during anticipation, when the type of trial was cued - a previously unstudied phase of the fMRI task. Anticipation of the need to avoid an aversive stimulus has been positively associated with activity in the ACC, ventromedial PFC (vmPFC) and striatum (Critchley, Mathias, & Dolan, 2001; Mobbs et al., 2007; Rzepa et al., 2017). These regions have been found to relate to cognitive processing of emotions such as fear, evaluation of context, vigilance and behavioural control (Amat et al., 2006; Critchley et al., 2004; Liotti et al., 2000; Mobbs et al., 2009; Schiller et al., 2008).

6.1.1 Hypotheses and aims

6.1.1.1 Neuroimaging sample

We hypothesised that anticipation of the need to avoid an aversive stimulus would be associated with increased activity in the ACC, vmPFC and striatum (Mobbs et al., 2007; Rzepa et al., 2017). It was expected that active avoidance in pursuit trials (relating to fear) would elicit activity in the vmPFC, cerebellum and PAG (Mobbs et al., 2007; Perkins et al., Under Submission) and that active avoidance in goal-conflict (anxiety related) trials would elicit hippocampal activation (Bach et al., 2014; Perkins et al., Under Submission). In our group comparison (patients versus controls from Study 1), the hypotheses were that: patients would show increased activation, compared to controls in the regions hypothesised for both anticipation and threat pursuit conditions. An equivalent prediction was made for the main effects of each condition and association with threat (a comparison between threat versus no threat trials).

As well as whole brain analyses, we conducted ROI analysis with the expectation that: 1) PAG activity would be positively associated with threat proximity and that 2) goal-conflict sensitivity would be associated with activation of the anterior hippocampus and that this activation would be positively associated with neuroticism, as per findings in the fMRI piloting of the JORT in healthy controls (Perkins et al., Under Submission).

Regressions explored the relationship between psychological variables in anticipation and flight phases of the JORT. These included post-task subjective dread ratings (which we hypothesised would relate to the anticipation phase and Risk Assessment Intensity on goal-conflict trials, (Berns et al., 2006), trait anxiety (STAI, which was hypothesised to relate to neural activity on goal-conflict trials) and fear (FSS tissue damage subscale, which was hypothesised to correlate with brain activation on pursuit trials) (Perkins et

al., 2013; Perkins & Corr, 2006; Perkins et al., 2007). Additionally, regressions between behavioural JORT performance and neural activation were explored. These behavioural measures included: Flight Intensity (the degree that signalled threat increased speed of movement in fear conditions) and Risk Assessment Intensity (the degree that signalled threat increased anxiety behaviour) along with average velocity on pursuit trials and average oscillations in movement on goal-conflict trials. It was expected that elevated JORT threat-avoidance behaviours would be associated with exaggerated activation patterns in the hypothesised regions.

6.1.1.2 Behavioural sample

Due to evidence that anxiolytic medication reduced threat-related behaviour on the JORT (Perkins et al., 2013; Perkins et al., 2009) and elevated sensitivity to threats being key features of affective disorders (LeDoux et al., 2017), higher Flight Intensity and speed of movement in pursuit trials, and Risk Assessment Intensity and oscillations in movement on the goal-conflict trials scores were expected in the patient group relative to controls (measures from participants in both Study 1 and 2 who completed the JORT task offline). Positive correlations between JORT behavioural measures and the following self-report measures were expected: neuroticism (EPQ-R), state dread and depression severity (MÅDRS), due to findings of elevated threat sensitivity in psychopathology (LeDoux et al., 2017). Additionally, positive correlations were expected between fear (FSS fear of tissue damage scale) and Flight Intensity, and trait anxiety (STAI) and Risk Assessment Intensity scores, in line with the differential directions of threat avoidance; fear being associated with flight behaviours and anxiety with risk assessment, as proposed in the reinforcement sensitivity theory (Gray & McNaughton, 2000).

6.1.1.3 Behavioural results with therapy

A subset of participants completed the task twice - both before and after a course of CBT (Study 2 participants). It was expected that patients would have lower Flight Intensity and Risk Assessment Intensity scores post- compared to pre-therapy due to CBT's aim of reducing anxiety, attentional focus and anticipation towards threats (Grupe & Nitschke, 2013; Hadwin & Richards, 2016; Maslowsky et al., 2010). Additionally, it was predicted that treatment responders would show a greater reduction in JORT Flight Intensity and Risk Assessment Intensity scores, as research has shown that the degree to which threat-avoidance reduces during treatment is a predictor of treatment outcomes in anxiety disorders (Legerstee et al., 2010, 2009). We also hypothesised that these patterns of reduction post-therapy would be found in self-report measures related to threat-avoidance (level of fear measured with the FSS tissue damage subscale, dread rating on the JORT, neuroticism and trait anxiety).

It was expected, due to evidence that those with higher levels of threat-avoidance and attentional-bias towards threats have poorer therapeutic responsiveness (Legerstee et al., 2009; Mogg & Bradley, 2016; Price et al., 2011), that treatment responders would have lower baseline Flight Intensity and Risk Assessment Intensity than non-responders to CBT.

6.2 Methods

6.2.1 JORT fMRI and behavioural paradigm

The fMRI task that Study 1 participants completed is illustrated in Figure 6-a. The participant viewed a two-dimensional linear runway presented on a computer screen whilst in the scanner (Figure 6-a, B). The task has four trial types: Pursuit; Pursuit plus

threat (of electric shock); Goal-Conflict; and Goal-Conflict plus threat (of electric shock). In Pursuit trials (Figure 6-a, C), the participant was instructed to squeeze a force sensing hand gripper to move a virtual agent (a green dot) along a runway fast enough to remain ahead of the moving predatory red dot so as not to get caught. The gripper was force sensing, in that the greater the force applied to the handle the faster the green dot would move, allowing the participant to control the dot's speed of movement. Half of the Pursuit trials presented to participants had a lightening flash symbol displayed in the corner of the screen (Figure 6-a, D). On these trials the participant would receive an electric shock to the right foot if the red dot caught up to the green dot (delivered on an MRI compatible electric stimulator with a choice of 8 shock levels). Before beginning the task, the participant calibrated the electric shock machine to a level that they found aversive but not painful (i.e. their own tolerance level, and no more than 80 Volts at 20 amperes). The goal-conflict trials comprised a second additional red dot which travelled above the green dot (Figure 6a, E). This required the participant to move the green dot cursor fast enough to avoid the pursuing red dot but not too fast that it would collide with the leading red dot. As with the Pursuit trials, at the start of the trial the chasing predator approached the agent requiring the agent to accelerate to an escape velocity. The second preceding agent would then appear on screen. The participant was instructed to keep the speed of the agent constant to avoid nearing one of the predators. The speed of the proceeding predator was kept constant but the preceding predator's speed varied to ensure this dot was always visible on screen. Again, in half of the goal-conflict trials, as with the pursuit trials, a lightening flash symbol was presented to let the participant know that they would receive an electric shock if they got caught by a red dot (Figure 6-a, F).

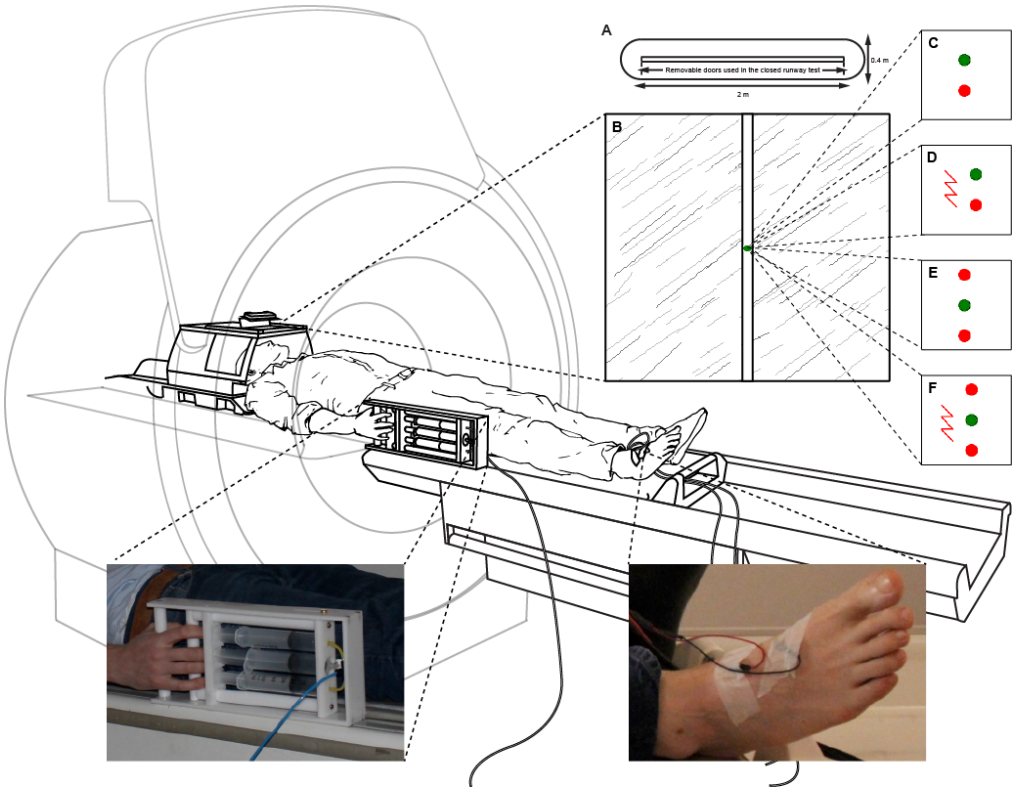


Figure 6-a: The fMRI Joystick Operated Runway Task (JORT).

The JORT (B: F) is a human translation of the Mouse Defence Test Battery (A). As illustrated, participants squeezed a force-sensitive interface to control the speed of a green dot as it was pursued on the runway by red dot(s) (B). If the red dots collided with the green dot, on certain trials an electric shock was inflicted. The task comprised 12 trials of each type: C) Pursuit; D) Pursuit plus threat of electric shock; E) Goal-Conflict; and F) Goal-Conflict plus threat of electric shock.

Therefore, in all trials the participant was instructed to avoid getting virtually caught by a predator which required tightly controlled regulation of speed. If the participant succeeded in not getting caught, after 7 seconds the predator(s) disappeared allowing the participant to decelerate to rest. If the participant was caught, the trial was terminated leading to variable trial durations for unsuccessful trials. However, in these unsuccessful trials, successive tests did not start earlier. Participants were presented with 12 trials of

each class, 48 in total, presented in a pseudo-randomised order and with inter-trial intervals varying between 15 to 30 seconds to heighten unpredictability. The task was 18 minutes and 14 seconds in total. Participants were instructed to continue to rest at the beginning of each trial until the chasing red dot appeared. If caught, the participant was not explicitly punished in low threat (safe) conditions but was with cued threats in high threat conditions.

The force-sensing hand gripper was set to require a force of 7.5 kilograms to keep the green dot ahead of the red dot. This level was chosen due to pilot testing which found this to be a generally appropriate level for participants over the course of 48 trials: effortful but without causing pain. In the behavioural version of the JORT, illustrated in Figure 6-b, the player controls the agent not through a hand gripper but a force sensing joystick that is individually calibrated according to physical strength to ensure the requirement of force for operation. These instruments were designed to mimic biological, real-world predatory threat scenarios where physical effort is required. The threat in the behavioural task also differed - the threat being an unpleasant loud burst of white noise, rather than an electric shock. Behaviourally the two phases of the task (Pursuit, Figure 6-b, B, and Goal-Conflict, Figure 6-b, C) are also repeated 24 times, half with and half without threat of noise, totalling 48 trials.

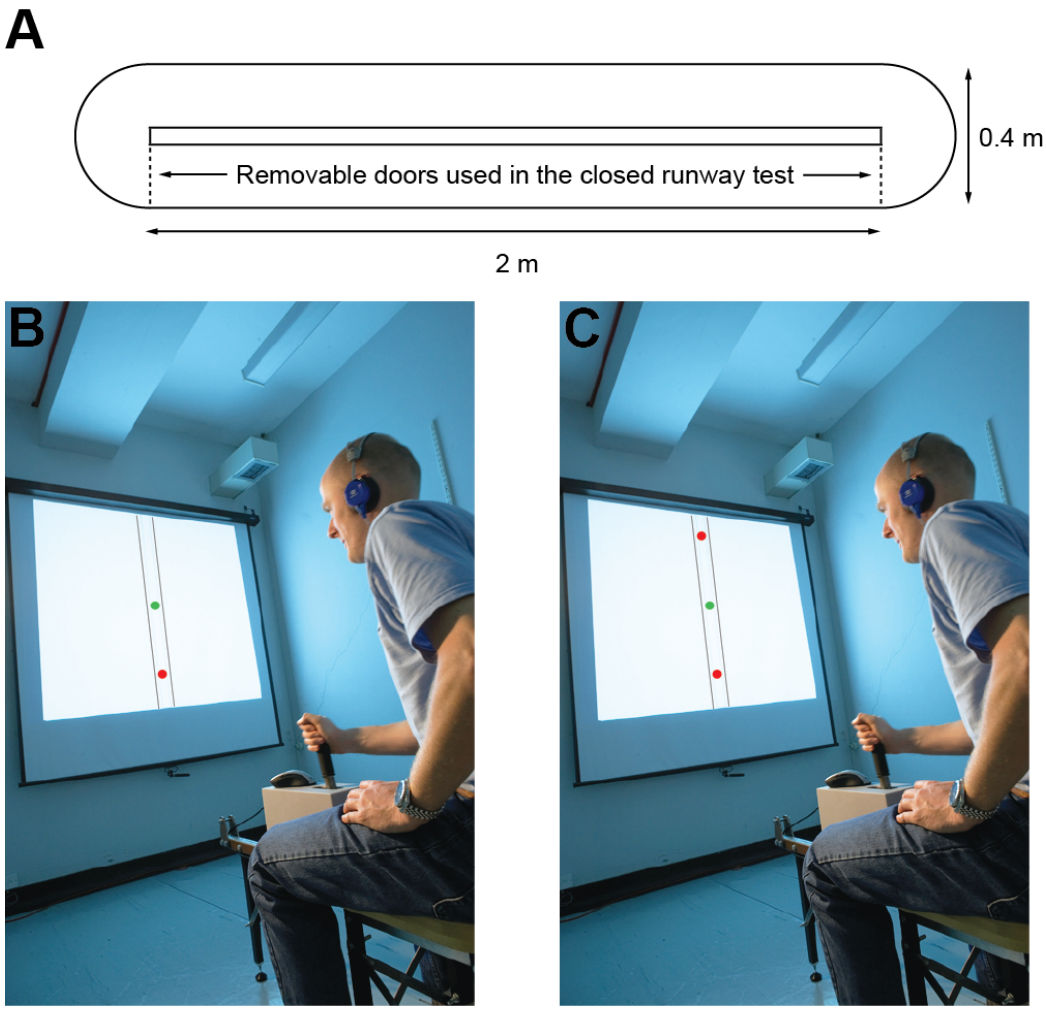


Figure 6-b: The behavioural human translation of the Mouse Defence Test Battery (MDTB, A): The Joystick Operated Runway Task (JORT, B and C).

All participants underwent a practice session before completing the JORT behaviourally or as an fMRI paradigm to familiarise subjects with the skill and force required to successfully complete the task. Multiple sessions were conducted if required.

6.2.1.1 Behavioural measures from JORT performance

The behavioural measures calculated from participant performance on the JORT and used in the analyses were calculated from the amount of pressure the participant applied to the joystick or hand-gripper and their resulting movement on the runway. These included:

Flight Intensity, which is the degree that the signalled threat (icon of lightning) increased the velocity of the participant controlled green dot during the pursuit trials (i.e. the average velocity of pursuit trials with threat minus the average velocity of pursuit trials with no threat). Risk Assessment Intensity, which is the oscillations in movement measured by the standard deviation of the average speed of movement in the goal-conflict plus threat trials minus the standard deviation of speed of movement of the green dot in goal-conflict without threat trials. Additionally, the average velocity of movement was calculated for pursuit trials (both threat and non-threat trials) and the average oscillations (standard deviation of speed of movement) calculated for goal-conflict trials (both threat and non-threat trials combined).

6.2.2 Psychological measures

Participants completed the following self-report questionnaires to allow examination of the association with these measures and JORT outcomes:

State dread rating: Upon completing the JORT, participants were asked to rate how much dread they had experienced whilst the red dot(s) were chasing them on a scale of 0 (no dread) to 10 (maximum dread).

Neuroticism, measured using Eysenck's Personality Questionnaire – Revised Version (EPQ-R), a 100 item self-report scale (Eysenck, Eysenck, & Barrett, 1985).

Trait Anxiety, via Spielberger's State Trait Anxiety Inventory, (STAI, (Lushene et al., 1970). This scale consists of 20 trait items scored on a 4-point Likert scale from "Almost Never" to "Almost Always" with higher scores indicated greater trait anxiety. For example, "I get in a state of tension/turmoil as I think over my recent concerns and interests".

Fear, via the Fear Schedule Survey (FSS): this measure has 108 stimulus items for which it is maladaptive to have more than mild anxiety in response towards, for example, fear of “fainting”, “kissing”, or “large open spaces” (Wolpe & Lang, 1964). Item scores are summed to give a total measure of fear proneness and subscales include an interpersonal, social fear subscale and fear of tissue damage (the latter of which has been found to be related to flight intensity on the JORT and a relatively pure measure of fear, Perkins et al., 2011, 2013).

6.2.3 Image analysis

6.2.3.1 Functional MRI acquisition

The functional sequence comprised T2*-weighted gradient EPI sessions of 543 whole brain volume acquisitions: flip angle 75°; TR = 2000 ms; TE = 30 ms; FOV = 24 x 24 cm; slice-thickness = 3 mm; inter-slice gap = 0.3 mm (total of 41 slices); matrix size = 64 X 64 voxels with an isotropic 3 mm x 3 mm in-plane resolution. A high-resolution T1-weighted image was also acquired as outlined in Chapter 3.

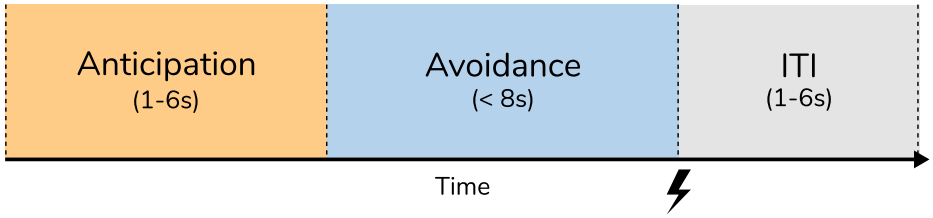
6.2.3.2 Functional MRI pre-processing

Data pre-processing was conducted using SPM-12. Images were realigned to the first image of the run, slice timing was corrected, and functional images were co-registered to the high-resolution T1 image. Segmentation and normalisation was performed on the T1 images and deformation fields were then used to normalise the functional images to MNI space. Smoothing was not performed at this step due to subsequent first level analysis which is best performed on unsmoothed data (Diedrichsen & Shadmehr, 2005). Realignment parameters were inspected and subjects demonstrating translation of over one voxel were excluded from further analysis. The first four volumes from each session were discarded to allow for magnetization equilibrium prior to acquisition.

6.2.3.3 First level analysis

First level analysis was performed using SPM-12 using a general linear model. Regressors for each trial type in this event-related fMRI paradigm were included for Anticipation (the time preceding the start of the chase when the type of trial was cued), Active-Avoidance (time during the chase by the red dot(s)), and the End of the Chase, split into trials where the subject was Caught and those where the subject Escaped. See Figure 6-c for an illustration of the trial timings.

Figure 6-c: Illustration of trial timings.



Abbreviations – ITI, Inter trial interval: S, seconds.

The following parametric modulators were also included: 1) Cumulative Threat, defined as the area under the curve of the participants' distance from the closest chasing stimulus; 2) Peak Threat, defined as the closest distance to either chasing stimulus during the trial; 3) Oscillation Amplitude (as a measure of threat assessment, anxiety-related behaviours), defined as the standard deviation of the participant's movement.

On some trials for certain subjects, the subject either failed to react to the trial or a technical issue with the force sensor on the hand gripper led to an absence of movement. These trials were excluded through inclusion in the model as nuisance regressors. Subjects whose data were unusable for more than four trials of any condition were excluded from analyses (therefore at least 8 trials for every participant in each of the 4 conditions were

required: Pursuit; Pursuit with threat; Goal-Conflict; Goal-Conflict with threat). This criterion was also used for behavioural analysis.

Given the risk of head motion induced by the electric shocks in the task, ensuring non-neural motion-related artefacts in the data did not influence the results was a priority. In addition to including motion regressors in pre-processing steps, we used further methods to reduce the impact of motion at the first level. Firstly, time points exhibiting high levels of motion were identified using the motion outliers tool included in the FMRIB software library (FSL, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) based on DVARS (Derivative of rms VARiance over voxels, which is a measure of how much the intensity of a brain image changes from one volume to the next) and framewise displacement measures (head movement from one volume to the next) (Power et al., 2012). Regressors for these time points were included in first level modules to exclude them from model estimation. Secondly, we used CompCor (Behzadi et al., 2007) to identify signals in the data likely representing signals of non-neural origin. Briefly, this involves extracting signal from white matter and cerebrospinal fluid (CSF) voxels, based on segmented T1 images, before using principal component analysis (PCA) to reduce the dimensionality of this data and produce a chosen number of components (six in this case) representing non-neural signals. These component time series were then included in first level models to reduce the impact of both motion and physiological arousal.

Finally, we estimated first-level models using robust weighted least squares (WLS) estimation. WLS down-weights the contributions of time points with high estimated noise to reduce the impact of motion on model estimation. As this step is best performed on unsmoothed data (Diedrichsen & Shadmehr, 2005), smoothing was subsequently applied to the contrast images produced by the first-level analysis with an 8mm FWHM Gaussian

kernel. First level contrasts of interest were taken forward to the second level for group-level analysis.

6.2.3.4 Second level analysis

Main task effects were evaluated in the control and patient group together to allow identification of systems involved in active avoidance and anticipation on this task overall. Group comparisons of patients versus controls were performed using independent t-tests. All analyses included total distance travelled, an index of subject-level motion, as a covariate. Group comparisons also included age and gender as covariates.

The primary contrasts were the task conditions (the anticipation phase when the type of task was cued and the active-avoidance phase when participants were being chased by a red dot in the goal-conflict and pursuit trials), both compared to the baseline resting condition (fixation on a cross). The following neural main-effects were explored in both anticipation and active-avoidance task conditions: 1) pursuit versus goal-conflict conditions; and 2) threat versus no threat (safe) trials. Additionally, in the active avoidance phases of the task, we tested: 1) whether activity in the active avoidance phase correlated with the level of oscillations in movement made, and 2) explored activity in the active avoidance phase correlating with how close the red dot predator(s) were, giving a measure of brain activity in peak threat.

Regressions explored the relationship between individual differences in clinical and psychological variables and neural activity in the anticipation and avoidance phases of the JORT. These included post-scan ratings of subjective dread and trait individual differences in proneness to negative emotions: neuroticism, trait anxiety (STAI), and fear (FSS, tissue damage subscale). The anticipation phase was correlated with trait anxiety, dread rating and an interaction between threat versus no threat trials. In the active-

avoidance phase, relationships between self-report trait anxiety and neural activation in goal-conflict trials were explored and self-report fear with activation on pursuit trials.

Our a priori hypotheses were to explore the degree to which trial to trial variation in PAG activity correlated with dread rating and trial to trial variation in peak threat (a measure of red dot proximity). Our second a priori hypothesis tested the sensitivity of the anterior hippocampi to goal-conflict. We correlated this with neuroticism scores, predicting that neuroticism would be negatively associated with hippocampal activity.

For the exploratory whole brain analyses, results were thresholded with a voxelwise, cluster-defining threshold of $p < .001$ and a cluster-level threshold of $p < .05$, family-wise error (FWE) corrected (Nichols & Hayasaka, 2003). This has been shown to be an appropriate level where the false positive rate is well controlled in SPM (Eklund, Nichols, & Knutsson, 2016). The bilateral hippocampal ROIs were generated using the WFU-Pickatlas toolbox (Wake Forest University) using automatic anatomical labelling (AAL). The PAG ROI was defined as per Mobbs et al., (2007; 2009) using the following co-ordinates with a 6mm radius, x = 4, y = -30, z = -24 in MNI space. The ROI analysis was conducted separately for each region with a small volume correction and a significance threshold of $p < .05$.

6.2.4 Behavioural analysis, comparison between patients and controls

Data were analysed using SPSS Version 24.0 (SPSS Inc. Chicago, US). Differences in group performance were assessed with independent-samples t-tests. Effects between JORT Risk Assessment Intensity, Flight Intensity, velocity on pursuit trials, and oscillations on goal-conflict trials and other measures relevant to threat avoidance (the FSS-tissue damage subscale, STAI, neuroticism and JORT dread rating) were assessed with Pearson's correlations.

6.2.5 Behavioural analysis with cognitive behavioural therapy

Repeated-measures ANOVAs with Greenhouse-Geisser correction were conducted to test whether patient scores on Flight Intensity, Risk Assessment Intensity, average velocity and oscillations differed pre- to post-CBT. This was conducted in all patients undergoing therapy and additionally with treatment response as a between subjects factor. Independent samples t-tests comparing responders versus non-responders on JORT behavioural measures were conducted on baseline and post-treatment data. Additionally, these analyses were conducted on JORT dread rating, self-report fear (FSS-tissue damage subscale), trait anxiety (STAI) and neuroticism.

6.3 Results

6.3.1 fMRI Results

Twenty patients and nineteen age and gender matched healthy controls completed the fMRI task from Study 1 (see Chapter 3 for eligibility criteria). One participant's data was removed due to excessive head movement and a further two participants' data were removed due to more than four trials with unusable data. Therefore, eighteen individuals with major depression and comorbid anxiety disorders, in addition to seventeen healthy controls' data, were included. See Table 6-a for participant characteristics.

There were no significant differences between patients and controls on the JORT's behavioural measures of Flight Intensity (effect size – Cohen's $d = 0.31$), Risk Assessment Intensity (effect size – Cohen's $d = 0.08$), average velocity (effect size – Cohen's $d = 0.29$) or average oscillations (effect size – Cohen's $d = 0.22$); however, the patients reported experiencing significantly more dread on the task (effect size – Cohen's $d = 1.27$).

Additionally, the patient group scored significantly higher on trait neuroticism, trait anxiety and fear proneness (FSS tissue damage).

Table 6-a Participant characteristics and JORT performance.

	Patient Group (n=18)	Control Group (n=17)	Comparison (patient versus controls)
Age (years)	30.4 (9.2)	32.4 (10.7)	t = -0.6
Gender (M/F)	7/11	7/10	$\chi^2 = 0.9$
MÅDRS	30.6 (7.5)	1.6 (2.0)	t = 15.8**
STAI – Trait anxiety	62.1 (7.8)	33.4 (6.1)	t = 12.0**
HARS	22.9 (6.2)	0.9 (1.3)	t = 14.4**
Dread Score	5.4 (2.8)	1.9 (2.7)	t = 3.8**
Neuroticism	20.3 (3.5)	6.8 (5.1)	t = 9.2**
FSS – tissue damage	49.0 (29.0)	23.9 (18.0)	t = 3.1*
JORT FI	.18 (.73)	-.07 (.86)	t = 1.0
JORT RAI	-.17 (.42)	-.14 (.27)	t = -0.3
Average speed on pursuit trials	9.0 (3.3)	8.1 (2.8)	t=-0.6
Average oscillations on goal-conflict trials	3.1 (0.5)	3.2 (0.4)	t=0.9
Number goal-conflict trials caught	17.9 (6.8) 74.5%	20.4 (6.8) 85%	t = 1.1
Number pursuit trials caught	1.1 (1.0) 4.6%	1.2 (2.2) 5%	t = 0.4

Values are reported as mean (standard deviation) except where otherwise stated. Comparison was by independent samples t-tests or Pearson chi-square for categorical variables. * Significant to $p < .005$ ** Significant to $p < .001$ ***Abbreviations – M, Male: F, Female: MÅDRS, Montgomery-Åsberg Depression Rating Scale: STAI, State Trait Anxiety Inventory: HARS, Hamilton Anxiety Rating Scale: FSS, Fear Schedule Survey: JORT, Joystick Operated Runway Task: FI, Flight Intensity: RAI, Risk Assessment Intensity.***

6.3.1.1 Anticipation phase of the JORT

The results in the following table are the second level analyses for the main effects of the anticipation phase of the task's contrasts including both patients and controls (see Table 6.-b and Figure 6-d). Only results that survived a cluster defining significance of $p < .001$ and a cluster-wise threshold of $p < .05$ FWE corrected are reported in the table, as per all whole brain results reported in tables throughout chapter. The tables (6-b and 6-c) include the significance level of the peak voxel within each cluster. The anticipation phase was associated with significantly elevated activation in two clusters including the right putamen / right anterior insula and left superior occipital gyrus / left cuneus and significantly reduced activation compared to baseline in right occipital, superior and temporal gyri. There were no significant main effects of neural activation in the anticipation phase correlating with condition type (i.e. goal-conflict versus pursuit trials). We did find a main effect of threat on neural activity: trials signalling the potential of an electric shock if caught were associated with elevated activity in the left superior frontal gyrus/dACC, right caudate, right superior frontal gyrus and supplementary motor area in the anticipation phase.

There were no correlations between self-report measures (neuroticism, trait anxiety, or subjective dread rating) and neural activity during anticipation. Nor any correlations with behavioural measures of JORT performance and any of the neural main effects.

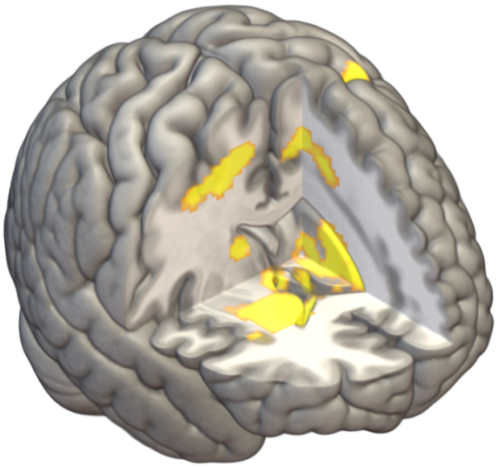
There were no significant results for group comparisons (patients versus controls) on any contrasts during the anticipation phase of the JORT.

Table 6-b: Joystick Operated Runway Task Brain Activation During Anticipation

Brain region	MNI Peak co-ordinates	*p of peak voxel*	Cluster size (voxels)	F	Direction
Anticipation (main effect of anticipation phase compared to baseline fixation)					
Right putamen (slightly into right anterior insula)	24, 10, 6	<.001	4058	133.0	Anticipation>Baseline
Left superior occipital gyrus / left cuneus	-18, -76, 34	<.001	9835	68.5	Anticipation>Baseline
Right occipital fusiform gyrus	22, -88, -10	<.001	7270	66.2	Baseline>Anticipation
Right superior/middle temporal gyrus	46, -16, -12	<.001	1284	36.4	Baseline>Anticipation
Anticipation and Threat (main effect of threat: threat versus no threat trials in the anticipation phase)					
Left ACC / superior frontal gyrus	-16, -6, 51	<.001	881	34.8	Threat>No Threat
Right Caudate	20, 26, 2	<.001	2196	32.2	Threat>No Threat
Right superior frontal gyrus / right pre-supplementary motor area	16, -4, 54	.022	378	30.3	Threat>No Threat

N = 35 (18 patients and 17 healthy controls). Significance was FWE cluster corrected. Peak coordinates are reported in MNI space. ***Abbreviations – MNI: Montreal Neurological Institute.***

Figure 6-d: Main effect of threat in the anticipation phase of the Joystick Operated Runway Task (p <.05 FWE corrected)



Abbreviations – ACC: anterior cingulate cortex; SFG: superior frontal gyrus; SMA: supplementary motor area. Blue regions denote decreased activation in threat versus no threat trials and yellow regions represent increased activation in threat versus no threat trials in the anticipation phase.

6.3.1.2 Active-avoidance phases of the JORT

Table 6-c details regions of significant activation in the active avoidance (goal-conflict and pursuit) phases of the task when participants were chased by the red dot predator(s). The main effect of both active-avoidance conditions (pursuit and goal-conflict trials combined) compared to baseline fixation showed elevated activation in prefrontal brain regions. A comparison between the active avoidance conditions (goal-conflict versus pursuit trials) showed significantly elevated activation in the left cerebellum, left orbitofrontal cortex and right anterior insula in pursuit trials compared to goal-conflict trials and elevated left anterior orbitofrontal cortex activation in goal-conflict compared to pursuit trials.

There was no significant main effect of peak threat (i.e. no correlation between activation in the flight phases of the task with proximity of the red dot predator(s) to the green dot agent). There was a main effect of threat (i.e. a comparison of trials with a threat of electric shock versus trials with no-threat of shock, see Figure 6-f). Threat trials were associated with significantly elevated activation in a cluster including the right insula and hippocampus. Safe, no threat trials were associated with elevated activation in prefrontal regions and the caudate. Further, striatum and middle temporal gyrus activity during avoidance was associated with Risk Assessment Intensity ($p = .003$ and .007, respectively), see Figure 6-g for direction of findings. There were no further correlations with psychological variables or JORT behavioural measures with brain activation for the main contrasts.

There were no significant results for group comparisons (patients versus controls) on any of the contrasts during the active avoidance phases of the JORT. There were no significant differences between the groups in the number of times they were caught by the chasing predators combined across all conditions ($t(33) = 1.04$, $p = .30$), suggesting ability did not confound results. However, there was a significant difference between the two threat-avoidance conditions as to whether participants were caught, participants being significantly more likely to fail to escape the predators in the goal conflict compared to simple pursuit trials ($t(34) = 14.6$, $p < .001$.

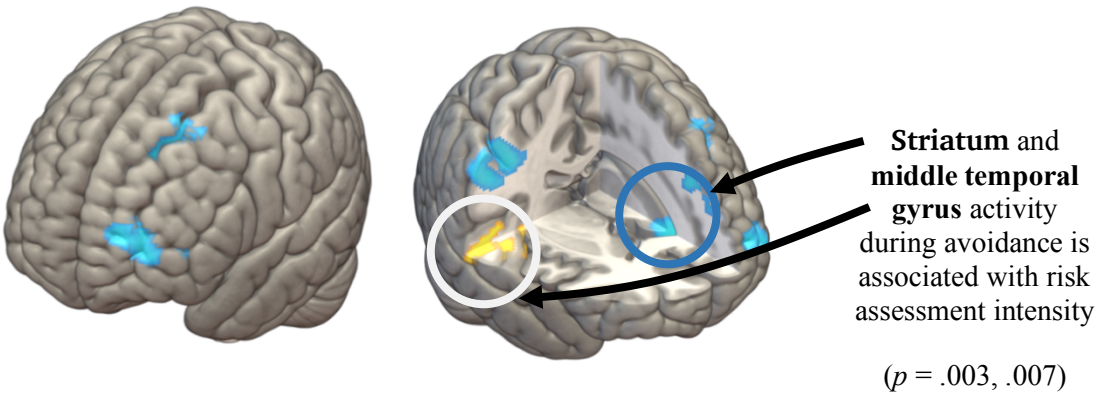
Table 6-c: Joystick Operated Runway Task Brain Activation During active threat avoidance (pursuit and goal-conflict)

Brain region	MNI Peak co-ordinates	*p of peak voxel*	Cluster size (voxels)	F	Direction
Main effect of both goal-conflict and pursuit active avoidance phases compared to baseline					
Right precuneus / superior parietal lobule	14, -52, 58	<.001	62177	339.1	Avoidance> Baseline
Left precuneus / posterior cingulate gyrus	-8, -54, 20	<.001	3043	102.6	Baseline> Avoidance
Left angular gyrus	-44, -64, 30	<.001	1485	90.5	Baseline> Avoidance
Right middle frontal gyrus	34, 40, 32	<.001	1464	82.3	Avoidance> Baseline
Left occipital pole, left calcarine cortex, left occipital fusiform gyrus	-16, -94, -6	<.001	797	60.4	Baseline> Avoidance
Left anterior orbitofrontal cortex	-26, 32, -16	<.001	4268	54.3	Baseline> Avoidance
Right lingual gyrus and right occipital fusiform gyrus	20, -88, -8	0.002	550	48.1	Baseline> Avoidance
Left superior / middle frontal gyrus	-20, 24, 44	<.001	810	36.1	Baseline> Avoidance
Pursuit versus goal-conflict trials main effect					
Left cerebellum	0, -66, -34	<.001	30141	67.69	Pursuit> Conflict
Right temporal and superior cortex	50, -32, 20	<.001	3290	51.40	Pursuit> Conflict
Left anterior orbitofrontal cortex	-22, 38, -10	<.001	1531	39.43	Conflict>Pursuit
Right anterior insula	40, 18, -10	.001	712	36.02	Pursuit> Conflict
Main effect of both goal-conflict and pursuit active avoidance phases correlated with the levels of oscillation in movement made					
Right precuneus, right superior parietal lobule	14, -52, 58	<.001	68267	209.09	Positive
Left & right precuneus and posterior cingulate	-8, -52, 18	<.001	2060	107.12	Negative
Left angular gyrus, left mid temporal cortex	-44, -62, 28	<.001	993	71.01	Negative
Right mid frontal gyrus	38, 44, 22	<.001	1413	49.88	Positive
Left occipital cortex	-16, -96, -4	.002	537	46.34	Negative

Right lingual gyrus, right occipital fusiform gyrus, right calcarine cortex	18, -88, -8	.011	329	45.02	Negative
Left anterior cingulate, left medial frontal cortex	-6, 44, -8	<.001	1255	34.40	Negative
Left temporal cortex	-56, -44, -14	.005	424	31.17	Negative
Left middle frontal cortex	-40, 38, 32	.007	375	29.82	Positive
Left orbitofrontal cortex (anterior / medial and posterior orbital gyrus)	-24, 34, -12	.013	306	29.81	Negative
Main effect of threat on neural activation in active-avoidance phase of the trial					
Left middle/superior temporal gyrus	-28, 56, 12	.004	562	37.07	Safe>threat trials
Left caudate	-16, 24, 2	.041	269	35.62	Safe>threat trials
Left frontal superior gyrus	-12, 38, 38	.005	489	35.17	Safe>threat trials
Right postcentral gyrus	42, -30, 48	.003	661	29.87	Safe>threat trials
Right posterior insula/ right hippocampus	40, -22, -4	.041	276	20.47	Threat > safe trials

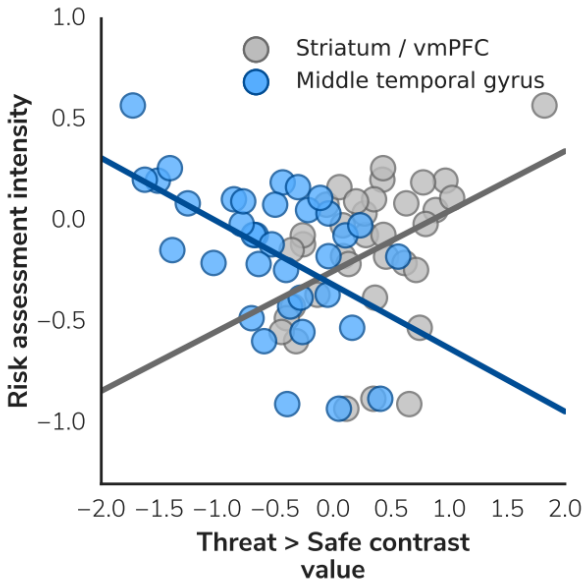
N = 35 (18 patients and 17 healthy controls). Significance was FWE cluster corrected. Peak coordinates are reported in MNI space. ***Abbreviations – MNI: Montreal Neurological Institute.***

Figure 6-e: Main effect of threat on neural activation in the active avoidance (flight phase) of the Joystick Operated Runway Task (p < .05 FWE corrected)



Abbreviations – FWE: family wise error. Blue regions denote decreased activation in threat versus no threat trials and yellow regions represent increased activation in threat versus no threat trials in the flight phase.

Figure 6-f: Joystick Operated Runway Task correlation between Risk Assessment Intensity and neural activation in active avoidance



Abbreviations – vmPFC: ventromedial prefrontal cortex. Analysis from peak voxel within each cluster.

6.3.2 Behavioural Results

Behaviourally, 29 participants (16 patients and 13 healthy controls from Study 1 and 2) completed the JORT task offline at baseline (see Table 6-d for participant characteristics and measures of task performance). Against expectations, no significant differences were observed between the patient and control group on any of the behavioural measures of JORT threat avoidance: Flight Intensity, $p > .05$, effect size – Cohen's $d = 0.13$; Risk Assessment Intensity, $p > .05$, effect size – Cohen's $d = 0.33$; average velocity, $p > .05$, effect size – Cohen's $d = 0.0$; or average oscillations, $p > .05$, effect size – Cohen's $d = 0.67$. However, patients did report experiencing more dread on the task when being chased by the red dot(s), $p < .05$, effect size – Cohen's $d = 0.88$. As would be expected, patients scored significantly higher on the MÅDRS, FSS tissue damage scale, STAI, and neuroticism measures.

Table 6-d: Behavioural participant characteristics and JORT performance, split by group

	Patient Group (n=16)	Control Group (n=13)	Group Comparison
Age (years)	36.9 (14.9)	32.5 (11.3)	t = 0.9
Gender (M/F)	6/10	4/9	$\chi^2 = 0.1$
MÅDRS	29.8 (6.6)	1.2 (1.5)	t = 15.3***
Anxiety (STAI)	63.9 (7.6)	31.5 (4.4)	t = 14.4
Dread Score	4.8 (3.2)	2.2 (2.7)	t = 2.3*
FSS tissue damage	44.4 (18.2)	23.6 (18.6)	t = 3.0**
Neuroticism	20.5 (3.6)	5.6 (4.6)	t = 9.8***
JORT FI	0.45 (0.63)	0.38 (0.45)	t = 0.36
JORT RAI	0.02 (0.15)	0.07 (0.18)	t = -0.81
Pursuit velocity	9.6 (0.8)	9.6 (0.4)	t = -0.3
Goal-conflict oscillations	4.3 (0.3)	4.1 (0.3)	t = 1.5
Number goal-conflict trials caught	8.8 (5.8) 36.7%	12.1 (4.7) 50.4%	t =-1.6
Number pursuit trials caught	1.1 (1.1) 4.6%	0.8 (1.4) 3.3%	t = 0.7

Values are reported as mean (standard deviation) except where otherwise stated. Comparison was by independent samples t-tests or Pearson chi-square for categorical variables. * Significant to p <.05, ** significant to p ≤.005, * significant to p <.001. *Abbreviations - M, Male: F, Female: MÅDRS, Montgomery-Åsberg Depression Rating Scale: STAI, State Trait Anxiety Inventory (trait score): FSS, Fear Schedule Survey: JORT, Joystick Operated Runway Task: FI, Flight Intensity: RAI, Risk Assessment Intensity.***

Bivariate correlational analysis was conducted to explore relationships within JORT measures and between trait anxiety (STAI), dread ratings, fear (FSS tissue damage), depression severity (MÅDRS), and neuroticism (Table 6-e). Significant positive correlations were observed in the patient group between: neuroticism and trait anxiety; neuroticism and dread rating of the JORT; depression severity and trait anxiety; and

neuroticism and oscillations on goal-conflict trials (a measure of anxiety behaviour). Significant negative correlations in the patient group were found unexpectedly between: depression severity and Risk Assessment Intensity; and trait anxiety and average velocity on pursuit trials. In the control group, negative correlations were found between Flight Intensity on pursuit trials and oscillations in goal-conflict trials, and dread rating and oscillations in goal-conflict trials.

Table 6-e: Correlations between the JORT and personality variables relevant to threat sensitivity, by group.

Variable	1	2	3	4	5	6	7	8	9
1 JORT FI	-	.35	.48	.22	.14	-.13	-.31	.17	-.81**
2 JORT RAI	.04	-	.33	.45	.27	.08	.14	-.20	-.32
3 Dread	-.34	.08	-	.51	.08	.09	-.03	.15	-.63*
4 FSS tissue	.14	.04	-.01	-	.32	-.07	-.05	.38	-.32
5 STAI	-.08	-.13	.38	-.09	-	.55	<.01	-.08	-.19
6 Neuroticism	-.18	-.13	.61*	-.08	.51*	-	-.03	-.45	.19
7 *MÅDRS*	.02	-.62*	.30	.14	.64**	.27	-	-.03	-.05
8 Velocity	.28	.10	-.06	-.16	-.590*	-.12	-.43	-	-.35
9 Oscillations	-.25	-.15	.23	.09	.449	.58*	.20	-.36	-

N = 29 (correlations for 16 patients in lower half of matrix, 13 controls in upper half). * *p* < .05 level ** *p* <= .01. *Abbreviations - M, Male: F, Female: MÅDRS, Montgomery-Åsberg Depression Rating Scale: STAI, State Trait Anxiety Inventory (trait score): FSS, Fear Schedule Survey: JORT, Joystick Operated Runway Task: FI, Flight Intensity: RAI, Risk Assessment Intensity.*

6.3.3 Behavioural results with treatment

14 patients (9 females) from Study 2 completed the JORT before and after a course of CBT (mean age 34.5 +- 14.4 years). The mean number of sessions of CBT attended was 10.7 (+- 3.0, range 6-16). See Table 6-f for participant characteristics, split by treatment response. Responders were significantly younger than non-responders and had received significantly more sessions of CBT. In terms of self-report measures, responders scored

significantly lower at both baseline and post-treatment assessment on the FSS tissue damage subscale (a measure of fear), and post-treatment scored lower on trait anxiety (STAI). There were no significant differences between responders and non-responders on JORT measures of Flight Intensity, Risk Assessment and oscillation intensity. There was trend for responders to show higher post-therapy average velocity on the pursuit trials compared with non-responders ($p = .051$).

Table 6-f: Sample characteristics, split by treatment response

	Responders (n=7)	Non-responders (n=7)	Group Comparison
Age, years	26.6 (6.1)	42.4 (16.2)	t = 2.4*
Male/Female (n)	2/5	3/4	χ^2 = 0.3
Baseline MÅDRS	30.7 (7.4)	27.9 (6.0)	t = -0.8
Number of CBT sessions	9.0 (2.5)	12.6 (2.3)	t = 2.8*
Baseline JORT FI	0.52 (0.42)	0.37 (0.42)	t = -0.6
Baseline JORT RAI	0.05 (0.20)	0.005 (0.11)	t = -0.5
Baseline velocity, pursuit trials	9.7 (0.5)	9.6 (1.0)	t = -0.2
Baseline oscillations, goal-conflict trials	4.2 (0.4)	4.4 (0.2)	t = 1.1
Baseline STAI	66.6 (8.8)	61.1 (5.8)	t = -1.4
Baseline Neuroticism	20.9 (4.3)	21.0 (3.1)	t = 0.1
Baseline FSS-tissue damage	32.6 (11.8)	51.3 (18.1)	t = 2.3*
Baseline Dread Rating	5.0 (2.3)	5.1 (4.0)	t = 0.1
Post-treatment JORT FI	0.29 (0.27)	0.59 (0.93)	t = 0.8
Post-treatment JORT RAI	-0.07 (0.11)	-0.002 (0.10)	t = 1.2
Post-treatment STAI	46.3 (5.5)	58.7 (7.8)	t = 3.4**
Post-treatment Neuroticism	17.1 (5.8)	20.3 (1.8)	t = 1.4
Post-treatment FSS-tissue damage	25.0 (10.1)	62.6 (21.5)†	t = 4.1**
Post-treatment Dread Rating	3.2 (3.5)	4.0 (3.2)	t = 0.4
Post-treatment velocity, pursuit trials	10.1 (0.8)	9.3 (0.6)	t = -2.2°
Post-treatment oscillations, goal-conflict	4.3 (0.2)	4.1 (0.4)	t = -1.2

†n=5 due to missing data for two participants. Values are reported as mean (standard deviation) unless otherwise stated. Comparison was by independent samples t-tests or Pearson chi-square for categorical variables. * Significant to p <.05 ** significant to p <.005, ° trend significant (p =0.051). ***Abbreviations - JORT: Joystick Operated Runway Task; MÅDRS: Montgomery-Åsberg Depression Rating Scale; CBT: Cognitive Behavioural Therapy; STAI: State Trait Anxiety Inventory; FI, Flighty Intensity; RAI: Risk Assessment Intensity; FSS: Fear Schedule Survey.***

Repeated measures ANOVAs on all patients (both responders and non-responders to CBT) showed no significant differences pre-to post-therapy on JORT Flight Intensity ($f(1,13) = <.001$, $p = 1$), Risk Assessment Intensity ($f(1,13) = 2.1$, $p = .17$), average speed in pursuit trials ($f(1, 13) = 0.006$, $p = .94$) or oscillations in goal-conflict trials ($f(1, 13) = 0.81$, $p = .39$). Subjective dread ratings also did not differ significantly over time ($f(1, 13) = 1.9$, $p = .19$), nor self-report fear (measures using FSS tissue damage scale, $f(1, 11) = 0.6$, $p = .45$). There was a significant reduction in trait anxiety (STAI) and EPQ-R neuroticism scores from time one to time two: $f(1, 13) = 9.0$, $p = .01$ and $f(1,13) = 6.2$, $p = .03$, respectively.

Including treatment response as a between subjects factor in the repeated-measures ANOVAs showed non-significant group by time interactions for Flight Intensity ($f(1,12) = 0.8$, $p = 0.39$); Risk Assessment Intensity; $f(1,12) = 1.8$, $p = .21$; average velocity of pursuit trials ($f(1,12) = 1.8$, $p = .20$); and subjective dread rating ($f(1,12) = 0.07$, $p = .79$). However, there was a significant difference from pre-to post-therapy between responders and non-responders in the oscillations in goal-conflict trials. Against our hypothesis, responders showed significantly higher levels of oscillation post-therapy compared to non-responders who showed a reduction: $f(1,12) = 5.6$, $p = .03$. There was a trend interaction ($f(1,10) = 4.1$, $p = .07$) for self-report fear with non-responders showing an increase and responders showing a decrease in FSS tissue damage score. Similarly, there was a trend interaction for neuroticism with responders displaying a greater reduction than non-responders ($f(1,12) = 3.3$, $p = .09$). There was a significant group by time interaction with self-report trait anxiety. Non-responders scored stably at the two time points but responders showed a decreased in STAI scores ($f(1,12) = 9.0$, $p = .01$).

6.4 Discussion

This chapter presents a psychiatric validation of the JORT, a measure of threat-avoidance that allows within-task, within-subject comparison of fear and anxiety (Perkins et al., 2009, 2011). Neural main effects of the task were found for both the anticipation and active avoidance phases of the task. However, no group differences, or correlations with self-report measures of threat-sensitivity were found. Against our hypothesis, the patient group were not found to score significantly higher than the healthy participants on JORT behavioural measures, though patients did report experiencing higher levels of dread whilst being chased on the task. No association was found between task measures and treatment response.

6.4.1 Neuroimaging results discussion

6.4.1.1 Main effects of task

Our results suggest that the JORT was effective in identifying neural systems involved in both anticipation and active avoidance of aversive stimuli. The key main effects of the task were that anticipation of avoidable aversive events was associated with significant activation in the ACC/superior frontal gyrus, insula and striatum, while active avoidance of aversive stimuli was associated with activity in prefrontal regions, the dACC and insula - regions which align with previous research (e.g., Mobbs et al., 2007, 2009; Rzepa et al., 2017).

More specifically during anticipation, trials signalling the potential of an electric shock were associated with elevated activity in the left superior frontal gyrus, right caudate, right superior frontal gyrus and supplementary motor area. This aligns with our hypothesis, and previous research suggesting that the ACC, supplementary motor area and striatum are activated with threat anticipation (Mobbs et al., 2007; Rzepa et al.,

2017). Mobbs et al. found that dACC activity was related to imminent threat, as opposed to distal threats, supporting our observed relationship with avoidance intensity. Our additional finding of supplementary motor activation in anticipation, a region involved in planning and initiation of movements, fits with other research involving threats of electric shocks (Maresh, Beckes, & Coan, 2013).

Our results offer support for a differentiation in the neural systems that govern the JORT's goal-conflict (anxiety-related) and simple threat avoidance (pursuit, fear-related) trials. Goal-conflict, compared to pursuit trials, resulted in significantly elevated activation in the left anterior orbitofrontal cortex and significantly reduced activation in the left cerebellum, left orbitofrontal cortex and right anterior insula, potentially signifying the increased attentional demands required in goal-conflict conditions. However, no correlations with behavioural measures of JORT performance or psychological variables were found on main effects in either the anticipation or active avoidance phases of the JORT. This limits our ability to draw conclusions regarding the reinforcement sensitivity theory – the defensive direction hypothesis whereby anxiety (threats that require approach, represented in the goal-conflict conditions) and fear (threats that need not be approached, i.e., pursuit conditions) - activate distinct brain regions and are associated with trait fear and anxiety measures.

We found a main effect of threat in that trials with threat of electric shock, compared to no-threat trials, resulted in increased activation in the right insula and hippocampus. Safe (no threat) trials were associated with elevated activation in prefrontal regions and the caudate. Further, elevated striatal and vmPFC activation and a reduction in middle temporal gyrus activity during avoidance predicted risk assessment intensity with threat. The elevated PFC activation in no threat trials may signify that on these trials the participants engaged in more higher order cognitive appraisal of threat-avoidance,

whereas in threat of shock trials the elevated insula and hippocampal activation may signify increased emotional reactivity, as would be expect towards threats (Mobbs & Kim, 2015).

In the piloting of the JORT as an fMRI task, no main effects of threat were found (Perkins et al., Under Submission). The difference between these results and the pilot study in healthy controls could be due to our inclusion of a patient group and the resulting variability in the included sample in terms of sensitivity to threat (both patients and controls were included in main effects analyses). Indeed, the sample included in the original pilot scored on average one standard deviation below normal on a neuroticism scale (Perkins et al., 2010), suggesting the task is not sensitive to threat in healthy individuals due to the mild level of threat the task presents.

We hypothesised that pursuit trials would activate midbrain regions, for example, the PAG, in line with findings from other threat-avoidance tasks (Mobbs et al., 2009, 2007). However, we were not able to replicate this finding either at a whole brain or ROI level. Additionally, our hippocampal ROI analysis did not show an association with goal-conflict conditions unlike previous findings (Abraham et al., 2013; Bach et al., 2014; O'Neil et al., 2015). Further, we found no association between brain activation and threat imminence. This goes against findings from Mobbs et al. (2007, 2009), which found that there is a switch from prefrontal to midbrain regions when threats are near, which they postulate to represent higher order appraisal of threats when they are far away and a switch to hard-wired defensive reactions when threats are close. It may be that our relatively small sample size lacked the power to find such effects. Additionally, the tasks used by Mobbs et al. (2009) involved the loss of a potential reward if caught and therefore this could explain the difference in results, as no reward was at stake in the JORT.

6.4.1.2 Patients versus controls

Although threat avoidance is primarily considered as a key trait of anxiety disorders, it has strong links to depressive symptomatology also. For example, Trew (2011) proposed a model of aberrant threat sensitivity processes in relation to depression which includes increased avoidance and decreased approach of threats which contribute to the development and maintenance of depression by the development of negative information processing biases and a reduction in exposure to potentially positive situations. There has been found to be an important role of both behavioural and cognitive avoidance in the maintenance of depression (Moulds et al., 2007; Ottenbreit & Dobson, 2004). Additionally, the relationship between neural activation on goal-conflict JORT trials and neuroticism in the fMRI piloting suggests a link to threat-related neural processes and depressive symptoms (Perkins et al., Under Submission). Therefore, there was justification for trialling this task in patients with depression and comorbid anxiety.

However, we did not find any significant differences in neural activation or behavioural measures on the task between our patient group and controls limiting conclusions and drawing concerns about the tasks sensitivity despite previous research by Perkins et al. (2009, 2013) finding differences in task behavioural measures in those with high versus low trait anxiety and fear and sensitivity to psychopharmacotherapy. It is possible that comorbid anxiety disorders, or overlapping symptoms between depression and anxiety may account for the relationship between threat sensitivity and depression. However, the relationship between threat-avoidance and depression has been found to remain after controlling for comorbid anxiety (Johnson et al., 2003), suggesting an important relationship between threat-sensitivity and depression, beyond that explained by anxiety symptoms and comorbidity. It is possible that our relatively small sample size and

inclusion of patients with typically mild to moderate depression severity limited our ability to find an effect.

The absence of significant differences in activation between patients and controls suggest that major depression is not associated with abnormal function in brain networks involved in active avoidance. Perhaps the concepts explored via the JORT are more related to pure anxiety disorders. A meta-analysis has shown that trait anxiety and fear of anxiety-related situations and threats was most associated with agoraphobia, GAD, panic disorder and PTSD compared to depression (Naragon-Gainey, 2010). Future research should trial the utility of the JORT in these patient groups where you would expect to see a more clear-cut elevation in threat avoidance. For example, patients with panic disorder (associated with fear and flight behaviours) would be expected to show elevated reactivity in pursuit trials, whereas patients with generalised anxiety disorder would be expected to show aberrant behaviour and neural activation on goal-conflict trials, associated with anxiety.

The JORT is an active, signalled avoidance task. It is active due to the requirement of action to avoid aversive events (passive/inhibitory avoidance tasks require withholding of behaviours to avoid aversive events) and signalled as the consequential threats are cued. Future research should investigate the basis of passive avoidance in major depression as self-report data comparing patients with depression versus healthy controls have shown elevated levels of passive avoidance in MDD (Pinto-Meza et al., 2006). Additionally, a study of tryptophan depletion (which allows investigation of the role of the serotonin system which is involved in the development and pathophysiology of depression (Donkelaar et al., 2011)) in healthy controls found that serotonin depletion caused participants to not respond appropriately to punishments in a passive avoidance task (Finger et al., 2007).

6.4.2 Behavioural results discussion

Higher scores in the patient group relative to controls were expected on all JORT behavioural measures of threat avoidance. Patients did report experiencing more dread on the task when being chased by the red dot(s) compared to controls but this did not translate to significant differences in the behavioural measures of the JORT between groups. This is problematic as a lack of empirical relationship between behavioural measures (e.g., speed of movement and oscillations) and the semantic value placed on these by participants limits conclusions (LeDoux et al., 2017). Additionally, this lack of association with self-report and behavioural measures was also found in the neuroimaging sample, limiting our understanding of the involvement of brain regions activated in the task.

We expected to find that all JORT behavioural measures (Flight Intensity, Risk Assessment Intensity, average velocity in pursuit and oscillations in goal conflict) and dread rating would be positively correlated with neuroticism and depression severity. We found significant positive correlations in the patient group between neuroticism and dread rating and neuroticism and average oscillations on goal-conflict trials (a measure of anxiety behaviour). These correlations were not found with trait anxiety or depression severity, suggesting neuroticism is more closely linked to threat sensitivity than other measures.

Positive correlations were expected between FSS fear of tissue damage and Flight Intensity, and trait anxiety (STAI) and Risk Assessment Intensity scores due to previous findings of this association (Perkins et al., 2011, 2013). These findings were not replicated in our sample. Unexpectedly, significant negative correlations in the patient group were found between: depression severity and Risk Assessment Intensity and trait

anxiety and velocity on pursuit trials. Additionally, in the control group we found a negative correlation between dread ratings and oscillations made in goal-conflict trials, suggesting that subjective dread did not increase but rather decreased anxiety related behaviour on the task.

Similarly, there was trend for responders to show higher post-therapy average velocity on the pursuit trials and significantly elevated oscillations in movement on goal-conflict trials compared with non-responders. This is the opposite of what was hypothesised as we expected responders to show a reduction in speed of movement (illustrative of a reduction in threat sensitivity) and a reduction in Risk Assessment Intensity (illustrative of a reduction in anxiety behaviours). In terms of group differences in oscillations, this may signify that treatment responders reacted more appropriately to predators post-therapy by making small oscillations to avoid getting caught, perhaps a sign of being less anxious about being close to approaching threats (rather than the proposition that this measure is positively associated with anxiety levels). The negative association between neuroticism and oscillations in healthy controls could also be explained by the same process. Regarding treatment increasing oscillations in responders, a key therapeutic aim of CBT is decreasing patients' avoidance from threatening stimuli, the increased oscillations in movement found in CBT responders post-therapy could be due to patients avoiding the red dots less and allowing closer approach of the predators. These results align with the findings of Perkins et al. (2013) where lorazepam was found to increase Risk Assessment Intensity in those with high trait anxiety scores.

As with previous studies exploring the effect of psychotropic medication on JORT performance, our results suggest that the reinforcement sensitivity theory and pathological responses separating anxiety and fear may be less clearly defined in humans compared to the animal models upon which the theory was developed. Additionally, the

JORT relies on motor precision, especially the goal-conflict trials, i.e., there is a relationship between precision and punishment probability. Evidence that anxiety is associated with reduced motor accuracy includes sports (Huber et al., 2015; Moore et al., 2015; Nibbeling et al., 2012), simulated driving (Wilson et al., 2006), and playing music (Yoshie et al., 2008). These impairments are found even if they are likely to increase the risk of threat (Rigoli et al., 2012). Group difference in motor precision may have led to not finding significant group effects and the elevated Risk Assessment in treatment responders post-therapy, potentially illustrating increased motor precision with treatment response. However, our lack of significant differences between patients and controls in the number of times they were captured by the red dot predators suggest this was not the case, or if it were, did not impede in overall performance on the task.

An alternative explanation could be that the JORT is unable to detect group or treatment related changes in MDD and comorbid anxiety. Despite evidence showing that threat-avoidance reduces with therapy (Grupe & Nitschke, 2013; Hadwin & Richards, 2016; Maslowsky et al., 2010), and that higher levels of threat avoidance and attentional biases are associated with poorer treatment outcomes (Legerstee et al., 2009; Mogg & Bradley, 2016; Price et al., 2011), research has found that only particularly severe biases in avoidance towards threats were associated with poorer treatment outcomes to CBT. Patients with an attentional bias towards mildly threatening stimuli pre-treatment (so called threat vigilance), responded better to CBT (Price et al., 2011). Similarly, research has found a relationship between threat-sensitivity and treatment response only with severe threat cues (Legerstee et al., 2010, 2009). Due to the JORT representing low-level threats, its ability to determine severe biases in threat avoidance may have been limited, and explain why the expected differences between treatment response and differences between patients and controls were not found.

Additionally, an fMRI study exploring threat orienting before and after CBT and antidepressant medication in patients with GAD, found that neural activation, but not behavioural changes, occurred with treatment (Maslowsky et al., 2010). Behavioural measures may therefore be less sensitive to treatment response.

6.4.3 Strengths, limitations and suggested refinements to the JORT

A strength of the JORT task is that unlike most paradigms exploring threat-sensitivity, the design of the task allows for the effect of threat imminence to be explored. Most tasks do not vary proximity (Buchel & Dolan, 2000). For example, Pavlovian conditioning, the most commonly explored paradigms in threat sensitivity research, when a neutral stimulus is paired with an aversive stimulus, do not vary imminence, especially in terms of distance. Temporally certain conclusions may be drawn about imminence from Pavlovian studies in terms of the time of presentation of the conditioned stimulus, but this is not amenable to neuroimaging timeframes as the stimuli are typically presented for only 2-4 seconds. Mobbs et al.'s work (2007, 2009) has been instrumental in showing the effects of threat imminence on human brain activity during pursuit – finding that the midbrain takes over from prefrontal activation when threats are near. However, unlike the paradigms used by Mobbs and colleagues to explore the effect of threat imminence in pursuit, the JORT has the advantage of also exploring goal-conflict, within-task and within-subjects (to our knowledge the first task to explore these behaviours within the same task).

As with all threat-avoidance paradigms in humans, the JORT cannot wholly represent naturalistic threats, especially when the participant is in a scanner where constraints such as the participant remaining motionless are required. In the JORT, as with other paradigms in threat-avoidance human research, there is a higher-order nature of the

threat of electric shock or burst of aversive noise in relation to the pursuit/goal-conflict scenarios presented on the screen, i.e., the threat-avoidance is symbolic rather than ecologically natural. Although the JORT is not analogous to real-world threatening events, the results show alignment with other threat avoidance and anticipation studies in humans and also the animal literature where highly replicable circuits are found, giving confidence that threat-avoidance is measured on the task (Gray & McNaughton, 2000; McNaughton & Corr, 2004; Mobbs & Kim, 2015). The physical effort required on the JORT, unlike many tasks of threat avoidance in humans (e.g., Bach et al., 2014; Mobbs et al., 2007, 2009), make the task more ecologically valid.

In the behavioural version of the JORT, the pressure-sensitive joystick is calibrated to each individual participant's strength. In the fMRI version, the hand-gripper is one size and set to one pressure for all participants. Future studies using the JORT should calibrate the hand-gripper according to an individual's hand strength and provide a range of sizes. This would control for confounds brought about by variability in hand size and strength which could have conceivably led to those with larger and stronger hands (which we did not measure) experiencing less anxiety on the trials. Due to an error in data collection, we were not able to collect autonomic measures of arousal such as sweating (skin conductance) or tachycardia (heart rate) whilst the participant completed the JORT task. This would have strengthened the work due to the relation of these measures with threat (Epstein & Roupenian, 1970). For example, (Mobbs et al., 2009) found that skin conductance levels were associated with the level of threat experienced in their pursuit task.

Additionally, task ability may have influenced results. Other goal-conflict tasks have matched the difficulty level to each participant's skill (Gonen et al., 2016; Mobbs et al., 2009). A key improvement to the JORT would be to titrate the difficulty of the goal-

conflict trials according to individual performance, as we found that participants were caught in the majority of goal-conflict trials but rarely in simple pursuit trials in the fMRI task. This difference was less extreme in the behavioural version of the task but there was still a vast difference in the number of times participants were caught between the trial types. The practice session could ascertain performance level to set an appropriate level of difficulty (e.g., as done by (Mobbs et al., 2007) or even better the difficulty could be dynamically adjusted to ensure all participants get 'caught' and receive electric shocks the same number of times both overall and also in relation to both the goal-conflict and pursuit conditions in order to match these conditions more closely in terms of skill and demand. This would additionally control for any reductions in motor precision that may further confound JORT results in patients with affective disorders (Huber et al., 2015; Nibbeling et al., 2012; Rigoli et al., 2012).

As well as post-task ratings of dread whilst being chased by the digital predators, it would have been a good idea to ask participants about their confidence in avoiding the predator, as done by Mobbs et al. (2009), which may have affected neural activation and dread ratings. A lack of confidence in ability may have led to 'learned helplessness' in some participants (Maier and Watkins 2005), where depression like symptoms arise if threats are perceived as being uncontrollable (Grillon et al., 2003). By asking participants about their confidence in controlling the virtual agent, this could have determined whether differences between perceived and actual success varied between patients and healthy controls, a similar construct as measured in the FIQT (see Chapter 4).

Further to this when comparing the goal-conflict and pursuit conditions, it is possible that the presence of another dot on the screen reflects increased attentional demands and increased processing of stimuli required on goal-conflict trials, in addition to the measurement of interest. To control for these trial type differences, additional stimuli

could be included in the pursuit trial to more closely match the goal-conflict condition, but which would not interfere with the subjects' aim of avoiding the pursuing dot. A solution would be to present two preceding red dots, instead of one, in pursuit trials which move at different speeds and periodically overtake one another. This would allow for greater certainty that the level of difficulty, number of stimuli, and attentional demands are not influencing results and adding additional stress to the goal-conflict condition.

For the aforementioned reasons, there is doubt about the validity of the findings from the goal-conflict condition of the JORT task. We did find significant differences between pursuit and goal-conflict conditions; however, this could be due to the higher level of skill and attention required to negotiate not getting caught by two dots. Due to limitations with the goal-conflict condition, and a lack of association with behavioural measures of JORT performance and measures relevant to threat sensitivity, we cannot make conclusions regarding the differentiation between fear and anxiety as being separable emotions controlled by different brain networks.

Additionally, the task is likely to have been interpreted differently by individual participants as experiential fear is subjective and participants are likely to place their own meanings and biases onto tasks (LeDoux et al., 2017). The finding of group differences (patients scoring significantly higher than controls) and a range of scores on post-task dread rating show the task is able to invoke differential levels of fear that are sensitive to pathology. However, this subjective experience did not translate into group differences in behavioural performance on the task. We therefore conclude that this measure is not suitable for patients with MDD. Additionally, the task may not be suitable for all pure anxiety disorders. Anxiety is complex and there are likely to be multiple facets of anxiety related to different threat-related contexts. In depression threats such as the one posed in the Fake IQ test, a threat to self-esteem, may be more relevant. In social anxiety, you may

not expect to find elevated threat-sensitivity on a task such as the JORT, but only maladaptive levels in social contexts. Therefore, tasks studying treat-processing generally may not be suitable across all affective disorders.

Further, the JORT represents a low-level threat. In the MDTB, of which the JORT is a human translation, the rodents were placed in a real-life threatening situation and will therefore have experienced high levels of threat – the mice did not know the chasing predator was anaesthetised and therefore there was a perceived threat of death. Human participants had context to the test and knew that they were engaging in a task which involved mild punishments. The rodents on the other hand were threat naïve. Additionally, this contextual knowledge may have led to an elevated level of sustained apprehension and anxiety throughout the testing session which may have clouded differences between threat and anxiety conditions. It is possible that group differences would have emerged on a task representing higher threat levels.

Other fMRI paradigms designed to measure goal-conflict (often called approach-avoidance behaviour) have involved a conflict between a reward (e.g., a monetary incentive) versus punishments (e.g., threat of losing rewards or getting caught by a predator) (Bach et al., 2014; Gonen et al., 2016; Mobbs et al., 2013). The conceptualisation of goal-conflict therefore differs somewhat in the JORT as the goal-conflict is created by the need to approach threats in order to not get caught; there is no additional reward to successfully negotiate the threat except from successfully completing the trial. However, both are valid interpretations of goal—conflict; situations that can cause anxiety due to the need to approach threats (Gray & McNaughton, 2000). In depression, reduced sensitivity to rewards and an enhanced focus on punishments are a common finding (Eshel & Roiser, 2010). A task involving potential rewards may therefore provide stronger effects in patients with depression than a task which simply involves

avoiding punishments. As well as looking at passive avoidance tasks in depression, active avoidance tasks involving rewards should be explored further in this patient group.

Un-signalled, unpredictable threats have been found to shower greater effects than predictable, signalled threats as used in the JORT (Grillon et al., 2004). Also, block designs, as opposed to event-related designs, as the JORT is, have been found to produce more robust findings (Grillon et al., 2004). This can in part be explained by sustained contextual anxiety throughout tasks involving threats. Studies have found exaggerated startle and anxious states throughout the durations of experimental studies in: major depression (Grillon et al., 2003), PTSD (Grillon & Morgan, 1999; Grillon et al., 1998), panic-disorder (Grillon et al., 1994), and those at high risk of developing anxiety disorders (Grillon et al., 1998). This may have limited our ability to detect differences between the two conditions of the JORT, which were presented in a pseudorandomised order. Perhaps hippocampal and PAG differentiations between goal-conflict and pursuit conditions and associations with trait self-report measures would have been found in a block design, supporting findings from studies which have compared pursuit and goal-conflict in separate tasks.

6.4.4 Overall conclusions

Our results suggest that the JORT was effective in identifying neural regions involved in avoidance and anticipation of aversive stimuli, with activation being linked to threat level. However, the work presented in this chapter does not support the relevance of the JORT in major depression, as no significant differences between patients with depression and healthy controls were found neurally or behaviourally on the task. We suggest the measure may be relevant to disorders associated with a greater sensitivity to global

threats, such as panic disorder and GAD and that passive avoidance should be further explored in depression.

Chapter 7: Discussion chapter

7.1 Summary of findings

7.1.1 Aims

The overall aim of this work was to explore two novel functional neuroimaging tasks and a new analysis technique for resting-state data in patients with depression and anxiety. Additionally, meta-analyses of the neural correlates and predictors of response to psychological therapies in depression and anxiety disorders were conducted to determine whether robust results exist currently in this literature. The novel tasks were designed to avoid inherent issues with existing measures of threat-avoidance and negative self-referential processing with the hope they would inform us about pathological neural processing of threat-avoidance and self-referential thoughts in patients with depression and comorbid anxiety. Additionally, the utility of these novel tasks was piloted behaviourally to determine associations with response to CBT.

7.1.2 Functional neuroimaging and psychological therapy

Findings from neuroimaging studies of treatment response may not be robust when considered independently: studies often have small sample sizes which make it difficult to find strong effects after applying multiple comparisons across the whole brain. Meta-analyses are therefore encouraged to improve statistical power (Button et al., 2013). Our meta-analyses present a comprehensive analysis of the evidence-base to date for the neural predictors and correlates of psychological therapy in depression and anxiety disorders.

We were able to demonstrate consistent functional brain changes across psychological therapies in depression and anxiety disorders. The most robust findings were significant post-therapy decreases in activation in the ACC/paracingulate gyrus, left and right inferior frontal gyrus and insula, relative to pre-therapy. The results are largely in agreement with neural models of improved self- and emotional-regulation following psychological therapy due the observed decreases in limbic activation, areas involved in emotional processing. However, our decreased prefrontal activation with therapy runs counter to the dual process model of psychotherapeutic action. There was only one significant cluster of activation that was predictive of symptom change which met our inclusion for robustness, located in the right cuneus, a region not identified by other reviews in the field. Previous research has shown that emotional processing activates the visual cortex (Mourao-Miranda et al., 2003) and therefore elevated activation in visual regions, such as the cuneus, during tasks involving symptoms provocation or emotional processing may signify greater emotional processing and threat vigilance, which facilitates better treatment outcomes (Price et al., 2011). We expected that elevated ACC activation would be predictive of greater symptomatic improvement. This region was significant as a predictor, but did not meet our criteria for robustness. More research on predictors of psychotherapeutic response is therefore required to provide reliable predictors of psychological treatment response across disorders.

Our work adds to growing evidence suggesting that the dual process model cannot fully account for the mechanisms of psychological therapies (Franklin et al., 2016; Messina et al., 2016). We propose that a model with greater complexity is required, as suggested by Willner et al. (2013) for antidepressant medication mechanisms. The neural activation changes associated with psychological therapies appear to be more complex than a linear relationship between prefrontal and limbic regions, as the dual process model proposes,

and there are likely to be compensatory as well as corrective changes in brain activation with psychological treatments. Future models should include decreased prefrontal activation following psychological therapies, as we found in our meta-analyses, and which have been linked to a reduction in self-reflective cognitions and traumatic memories.

7.1.3 Self-reflection and the Fake IQ test

We piloted a novel task to measure implicit self-reflection: the Fake IQ test. We found that the measure was sensitive to psychopathology with elevated negative self-comparison to others, higher self-dissatisfaction, and lower perceived success in patients with depression and anxiety relative to controls on the task. Importantly, the 'fake' nature of the task did not appear to have been perceived by participants in post-task questioning and was not revealed quantitatively, which could have been demonstrated by increasing or decreasing levels of task satisfaction over the blocks if the participant had guessed they were completing an impossible task and altered their responses accordingly. We therefore propose the FIQT as an alternative to traditional self-report measures of self-reflection, with application to multiple patient groups associated with abnormal self-reflection. As we found no significant correlations between FIQT subscales and measures of depression severity, self-report self-criticism, rumination or worry, we have not shown evidence of construct validity. Further work should explore the task's relationship to alternative measures of self-reflection in order to validate the measure's construct validity, for example self-blame and perfectionism: constructs that are likely to be involved with perception of task performance.

Piloting of the task as an fMRI paradigm revealed that self-reflection on task performance invoked activity in brain regions involved in error-processing as hypothesised due to being a common finding with tasks of self-reflection. This adds some support to the measures

construct validity in measuring self-perception, reflection and error-processing. Specifically, we found increased activation on self-reflection versus control conditions bilaterally in the inferior cortex, insula, dlPFC, motor cortex and dACC. However, there were no significant differences between patients versus controls in neural activation on the task, nor correlations between brain activity and self-report measures of self-reflection.

7.1.4 Self-reflection and dynamic functional connectivity

Our study showed that major depression was associated with increased temporal variability in connectivity between two key DMN regions, specifically the mPFC and PCC. A key strength of this study was that we were able to replicate the finding in a second sample of patients with MDD free from comorbidity, suggesting the finding is robust. We found a positive correlation between connectivity variability and self-report rumination in one sample and therefore speculatively elevated negative self-referential cognitions may underlie this elevated temporal instability.

We believe the result represents an abnormality in network-specific neural properties in psychopathology rather than being an effect of global instability or underlying static connectivity differences due to our analyses in control regions and static connectivity which revealed no group differences. This work highlights the importance of studying dynamic functional connectivity to gain a more fine-grained representation of network abnormalities than static functional connectivity studies provide in this field.

Indeed, dynamic functional connectivity is a growing field of interest as, since the publication of this chapter (Wise et al., 2017), several studies have been published in psychiatric disorders including patients with major depression (Demirtas et al., 2016), bipolar disorder (Nguyen et al., 2017) and chronic fatigue (Boissoneault et al., 2016) and

those who have experienced childhood trauma (Cisler, 2017). For example, (Demirtaş et al., 2016) compared dynamic functional connectivity between patients with MDD (n=27) and healthy controls (n=27), as our study did. They found decreased dynamic functional connectivity within the DMN and fronto-parietal regions; however, no significant findings were found between the mPFC and PCC (the regions we focused our analysis on). Again, as with the previous study in MDD by (Kaiser, Whitfield-Gabrieli, et al., 2015), their whole brain approach (and additional small sample size) may have lacked the power to detect a significant difference between the mPFC and PCC. Additionally, a study (albeit in healthy controls) suggests dynamic functional connectivity may be sensitive to psychological treatments (Komulainen et al., 2017). A single dose of mirtazapine was found to alter dynamic functional connectivity in cortical midline structures and regions involved in emotional processing, including the insula, striatum, thalamus and hippocampus. A study in euthymic patients with bipolar disorder, compared to controls, found alterations between our regions of interest: the mPFC and PCC (Nguyen et al., 2017). However, they found the opposite direction of results to us; decreased dynamic functional connectivity in the patient group. This could be due to their patient group being currently euthymic or could represent a differentiation between unipolar and bipolar pathology. Further work is warranted to explore the relationship of the findings to bipolarity and treatment response.

7.1.5 Threat-avoidance

Behavioural and fMRI piloting of the JORT was conducted - a task yet to be piloted in patients with anxiety and depression despite abnormal anticipation and avoidance of threats being a key feature of affective disorders and the task having been validated in healthy controls (Perkins et al., 2009, 2011, 2013, Under Submission). In the behavioural piloting of the task, no significant differences were found between patients versus

controls, nor were any differences found between responders and non-responders to CBT or changes in performance pre- to post-therapy. Despite finding a significantly elevated subjective experience of dread in the patient group whilst completing the task, these results suggest that this subjective experience did not translate into significantly different behaviour on the task thus questioning the measure's sensitivity and validity to depressive pathology or experiential threat. Similarly, fMRI analysis showed no significant differences in neural activation on the task's conditions in patients versus controls. We conclude that passive avoidance may be more relevant to depression and warrants further investigation. Recommendations for refinements to the JORT task are made in Chapter 6, after which exploration should focus on disorders with a greater link to threat-sensitivity, such as GAD or panic disorder as we were able to demonstrate that the task conditions activated brain regions involved in anticipation and avoidance of threats.

7.1.6 Threat avoidance and negative self-reflection as distinct forms of threat

We measured physical threat with an active measure of defensive avoidance behaviours (the JORT). However, negative forms of self-reflection can also be considered as defensive responses albeit to more abstract perceived threats and generally resulting in more submissive defensive responses.

Self-criticism involves focusing one's attention on perceived personal faults, mistakes, and negative attributes with the consideration that there may be negative consequences, for example, punishment or negative social judgement (i.e. a threat to the self or a social threat). In affective disorders, high levels of negative self-reflection, for example self-blame, can be considered as a learnt defensive reaction in response to perceived conflict with others (Gilbert & Irons, 2005). High levels are associated with childhood trauma, in particular emotional abuse, furthering support that this is a learnt defensive reaction (Gilbert & Procter, 2006; Irons et al., 2006).

When a highly self-critical individual is asked to be self-reassuring, they have been found to respond with threat like responses - such as increased heart rate and skin conductance (Epstein & Roupenian, 1970) and patients with depression have been found to have deficits in self-soothing even when remitted (Gilbert & Procter, 2006; Rockliff et al., 2008). For example, in a neuroimaging task which involved hearing maternal criticism and being instructed to be self-reassuring, patients who were recovered from depression had altered neural activity compared to healthy controls, together with increased heart rate (Rockliff et al., 2008).

Therefore, just as with more physical threats i.e. the threat of an electric shock, self-criticism has been found to lead to similar bodily reactions and perhaps therefore also to brain activation associated with threat processing. We provide some support for this in our task of self-reflection as the regions activated in the FIQT aligned to those involved in error processing and there is some overlap between these regions and those involved in threat-avoidance. For example, on both the JORT (measuring threat-avoidance) and FIQT (measuring self-perception) we found insula, ACC and prefrontal brain region activation. The type of threat processing involved in self-reflection may be a more trans-diagnostic concept and therefore suitable to study in a broader range of psychopathologies. Indeed, a spectrum based model has been proposed by (Philippi & Koenigs, 2014).

7.2 Methodological considerations

7.2.1 Methodological approach

A key strength of the work presented in this thesis is that we looked at behavioural performance alongside functional imaging. The development of robust behavioural measures to link key aspects of pathological functioning, for example, deficits in

emotional processing and cognitive deficits, with specific neural circuitry could be an important step in achieving a more evidence-based methodology to psychiatric treatment. As a neuroimaging approach is expensive, well-designed behavioural measures that span several psychopathologies and that are linked to treatment response could be useful in clinical practice in their own right. The tasks we used in this body of work, namely the FIQT and JORT, are both implicit in nature and therefore avoid issues with self-report measures which may be biased or inaccurate (as discussed in Chapter 4). Neuroimaging can potentially help validate the behavioural measures, in terms of understanding their neural correlates, as well as providing information on the mechanisms of disease and recovery processes, and enabling the prediction of likely response to treatments.

7.2.2 Clinical Samples

A key strength of the patient group included in Study 1 is that we controlled for treatment effects: all participants were both medication-free and not currently undergoing psychological therapy at the time of scanning. Otherwise, we chose to include a naturalistic patient sample to pilot our novel methods due to the trans-diagnostic relevance of the measures under investigation. Our inclusion of patients with comorbid depression and anxiety disorders, nonetheless, limits our ability to determine which disorder(s) are responsible for our findings. Limiting to clinically pure populations without comorbidities would have allowed us to have greater certainty that the results are associated with specific conditions, as mechanisms may vary in those with comorbid diagnoses. On the other hand, it is important for neuroscientific research into affective disorders to include naturalistic patient samples, as if findings are to have translational relevance for clinical practice, effects are required in real-world samples who vary markedly in their clinical presentation, degree of severity, and psychiatric history. Indeed, MDD most commonly presents as being comorbid with other Axis I disorders (Kessler et

al., 2003). Larger sample sizes would allow for the influence of heterogeneity to be studied without relying on recruiting highly specific, un-representative clinical samples.

In line with the study's naturalistic design, the subset of patients who received CBT was selected from local psychological therapy service wait lists. The therapy received by participants was therefore representative of real-world therapy as we did not protocolise a course of treatment. Indeed, there was variability in the number of sessions that participants received: mean 11.61 (+-4.98), range: 6-28. Patients who responded to CBT typically received fewer sessions than those who did not respond, suggesting that CBT treatment is tailored according to individual need in normal clinical practice. However, the naturalistic, uncontrolled nature of the therapy received by participants may mean that it was sub-optimally delivered which may have reduced the chance of finding effects and have contributed to finding no associations between the tasks and CBT.

7.2.3 Resting-state versus task-based functional neuroimaging

The two novel functional imaging tasks we piloted, measuring self-reflection and threat-avoidance, were not able to demonstrate significant differences in brain activation between patients and healthy controls. We were, however, able to demonstrate group differences in our resting-state analysis. Resting-state scans have the following advantages over task-based paradigms: they avoid task-related confounds such as performance level, floor or ceiling effects; issues with practice effects in longitudinal studies involving repeated task-based fMRI sessions; and they evade the need for effort which may be an important consideration in certain patient groups (Fischer et al., 2016; Fox & Greicius, 2010; Whitfield-Gabrieli & Ford, 2012).

Additionally, despite the logical expectation that unconstrained thought during a resting-state scan may lead to a great diversity in the brain regions engaged, research has shown

a consistent neural network to be activated during rest: the DMN (Raichle et al., 2001; Shulman et al., 2007). This well-defined and measurable network, which has been found to be altered in affective disorders (Whitfield-Gabrieli & Ford, 2012), therefore has some advantages in comparison to task based measures which may introduce greater neural variability.

For example, the JORT (see Chapter 6) required a level of skill and between-subject variability in how difficult participants found the task will likely have caused confounds. We suggest that going forward the difficulty of the JORT should be calibrated to individual performance levels to ensure performance effects are controlled for. Regarding the FIQT, despite there being no right or wrong answers, the participants did not know this and therefore between-participant variability in prior knowledge of how they usually perform at these types of tasks could have confounded results. It would be interesting to test the task on healthy controls who know from experience that their performance on these types of cognitive, IQ-related tasks are poor to see if despite this they score more positively in self-referential questioning on task performance compared to patient groups. Additionally, a 'real' test of visual perception could be gained in addition to the FIQT at testing sessions to control for performance, IQ related-confounds in analyses: gaining a purer measure of differences in perceptions versus performance. This would help validate the task in terms of concurrent validity i.e. its ability to distinguish between patients and controls.

7.2.4 Meta-analyses

Although the meta-analysis technique used in this thesis is robust, and has numerous advantages over alternative neuroimaging meta-analytic techniques (Radua et al., 2012), the work relies on the quality of included studies. The analyses illustrated considerable

heterogeneity in the methodologies of the existing literature, a lack of replicability and small sample sizes. The results of the analyses are therefore likely to have been affected by limitations in the original studies.

Moreover, the meta-analyses in this thesis relied on reported peak co-ordinates in the studies, which provide only limited information about the exact results. Valid meta-analyses can be performed on such data, nevertheless inclusion of statistical parametric maps from the original studies can markedly improve sensitivity (Radua & Mataix-Cols, 2012). These three-dimensional images of results are rarely available, limiting the inclusion of studies. Researchers should share statistical parametric maps online via repositories such as Neurovault, making it simpler for future meta-analyses to include these maps in their analyses.

This field of research would benefit from studies with larger sample sizes, comparing various subtypes and diagnoses with a standardisation of design across research groups to allow understanding of the heterogeneity in results. Recommendations of best practice have been made for this field of research - the neural correlates and predictors of treatment response (Frewen, Dozois, & Lanius, 2008). Frewen et al.'s suggestions to improve the methodological rigor of the field include scanning both patients and a non-psychiatric control group at both baseline and post-therapy, along with a therapy control group also scanned at two time points. A therapy control group would allow greater confidence that the results illustrate the effects of therapy, by controlling for the passage of time and practice effects, similar to placebo arms in pharmacological studies. For example, Hölzel et al. (2013) included an active control intervention (the active therapy under investigation being mindfulness-based stress reduction). The control therapy was called stress management education and was designed to extricate the specific effects of mindfulness-based practice from other potentially effective elements of the therapy. They

recommend that both resting-state and task-based functional paradigms should be utilised and behavioural data collected during and immediately after scanning (as we did for all of measures, except resting-state which we acknowledge as a limitation hindering conclusions being drawn about the relationship of our findings to self-referential thoughts). They add that this behavioural data, including reaction times and physiological data, should be correlated with neuroimaging data.

Frewen et al. 2008 summarise that very few studies meet these criteria. In addition to their recommendations, we add the importance of making results available on online repositories and reporting whole-brain data as well as ROI results. Additionally, longer term follow-up, as well as scans throughout the duration of therapeutic trials, are required. This would enable us to more rigorously test the dual process model to determine whether there are differential primary effects between pharmacological and psychological therapy processes as the theory proposes. Additionally, more complete testing of neuroimaging paradigms is required to determine their validity and robustness before research teams adopt consistency in their study designs. Studies should also measure the quality of psychological therapy received, for example, the quality of patient-therapist relationships and the patient's engagement in both treatment sessions and homework should be recorded, as these are important predictors of response (Gomes-Schwartz, 1978; Lambert & Barley, 2001).

Although not within the scope of our prediction meta-analysis, another way to explore prediction of treatment response is to use pattern recognition methods such as support vector machine learning or transductive conformal predictors (Costafreda et al., 2009; Costafreda et al., 2009; Fu et al., 2008; Marquand et al., 2008; Nouretdinov et al., 2011). These methods have been found to have high predictive accuracy for response at the individual patient level and may be required in order to translate findings into clinical

practice. For example, Fu et al., (2008) found 86% accuracy in classifying patients' treatment response, prior to the initiation of treatment, using patterns of brain activity on an implicit emotional processing task.

7.3 Clinical implications

Many studies have discussed the potential of neuroimaging biomarkers to aid understanding of psychopathology and improve clinical decisions. Although developments in the field have been made in identifying the neural circuitry associated with depression and anxiety, we are a long way from translating this knowledge into robust biomarkers for clinical practice to improve treatment interventions and better tailor therapies to individuals according to likely response. Diagnosis remains based on patient self-report and clinical observation with the aid of DSM and ICD diagnostic systems. Transitioning our knowledge into clinical practice could take several complementary forms by utilising functional neuroimaging. Resting-state and task-based studies could be moved away from a group-based approach to become a tool for clinical decision making on an individual patient level. This may provide more accurate diagnoses and tailored treatment approaches for patients in the future – with disorders being characterised by deficits in neural circuitry, which may give more accurate classification than current diagnostic tools and lead to treatments targeting these connectivity and activation abnormalities (Fischer et al., 2016).

The work presented in the meta-analyses in Chapter 6 suggest that there are consistent neural activation changes occurring with psychological therapies across both depression and anxiety disorders, making these regions an interesting target for future biomarker development; although such methods are far from ready for use in clinical practice in

their current state. Replication of findings is required in larger and heterogeneous samples in order to validate their robustness across and between disorders. Additionally, the behavioural measures used in neuroimaging studies could be utilised in clinical settings, for example those exploring negative self-referential processing, to better target treatments. The work presented in Chapter 4 adds to a growing body of evidence that negative self-referential processing is a key feature of psychopathology which is linked to treatment response.

Despite our lack of findings between patients and controls in the fMRI version of the FIQT, our elevated dynamic functional connectivity in patients relating to rumination, and behavioural data from the FIQT and other self-report measures of self-reflection suggest there are abnormalities in negative self-referential processing which can be measured behaviourally and are related to a distinct brain network. Due to these concepts being relevant to most psychological disorders, targeting treatments more specifically to deficits in specific aspects of negative self-referential processing could be a key step towards improving treatment response.

These aspects of self-referential cognition could be measured in patients during clinical assessments via self-report and behavioural measures to lead to more targeted and personalised therapies. Indeed, in recent years numerous psychological therapies have been developed with an emphasis on targeting aberrant self-reflection including acceptance and commitment therapy (Hayes et al., 2013), acceptance-based behavioural therapy (Roemer et al., 2008), mindfulness-based cognitive therapy (Zindel et al., 2002), rumination-focused CBT (Watkins et al., 2011), and emotion regulation therapy (Fresco et al., 2013). In this thesis we were able to demonstrate that self-report measures of self-reflection were able to predict treatment response and showed significantly greater reductions in CBT responders compared to non-responders. However, FIQT measures did

not show significant reductions post-compared to pre-therapy, nor were there differences in responders or non-responders on the FIQT at baseline. Potentially, more targeted treatments would change directive task-based measures of self-reflection, such as the FIQT.

As negative self-referential processing often remains post-treatment and is associated with poorer response trajectories (Mennin & Fresco, 2013; Nolen-Hoeksema, 1991; Riso et al., 2003), tasks such as the FIQT which directly measure self-reflection may therefore serve a complementary purpose, in addition to self-report measures, in clinical practice. They could help to determine whether self-reflective responses to specific events and direct measures of performance have changed and not just an experiential reduction as would be demonstrated via self-report questionnaires. Rumination-focused CBT and emotion regulation therapy in particular directly target negative self-referential processing and train individuals to gain awareness of their negative processing (Fresco et al., 2013; Watkins et al., 2011). In combination with mindfulness-based meditation, this early cue detection can reduce negative self-referential perspectives in actions towards events (Mennin & Fresco, 2013). There is evidence that more targeted therapies could help prevent relapse and narrow the gap in treatment efficacy for those patients with higher levels of negative self-referential processing. Similarly, measures of self-reflection could be used to signal whether preventative measures or a longer course of treatment are required.

Additionally, our dynamic functional connectivity analysis in Chapter 4 suggested that alteration in functional connectivity in the DMN (related to self-referential processing) in depression goes beyond static connectivity differences. Further studies are warranted to see if treatments alter this temporal variability and further explore the relationship of temporal variability to self-referential processing. The DMN may be a potential target for

new treatments, for example, transcranial magnetic stimulation or new drug treatments (Fischer et al., 2016).

7.4 Future directions

7.4.1 The neural basis of psychological treatment response

The field of research into neural correlates and predictors of treatment response in affective disorders would benefit from studies using larger sample sizes, consistent study designs and analytic strategies. This would enhance the speed of discovery of clinically useful neural biomarkers. A large-scale trial is underway to discover the biomarkers in relation to antidepressant medication (Lam et al., 2016); however, a similar study for psychological therapies would be beneficial for these comparatively understudied treatments in neuroimaging research.

Additionally, in the work presented in our meta-analyses, causality cannot be inferred. Techniques such as dynamic causal modelling of fMRI data or neurostimulation alongside functional imaging would allow us to determine the causal direction of results. For example, TMS allows for the manipulation of specific brain regions over the duration of seconds or weeks, and their connected neural networks. Combined with neuroimaging, this would allow interpretation of the effects of manipulation (Etkin, 2017). For example, it has been found that the DMN, which is most active during rest, is differentially deactivated by different brain regions during attentionally demanding tasks (Chen et al., 2013).

Understanding in psychiatry is beginning to develop away from solely descriptive disease classification, aided by established diagnostic systems, to a system with greater biological

underpinning. However, given the complexity of the neural systems that underlie psychopathology, characterising quantifiable and objective psychiatric biomarkers has been more protracted than other fields of medicine, with much of the work in this field being un-replicated currently. The goal of biological-based, precision psychiatry is to understand the mechanisms and recovery processes within and between disorders, to identify resilience and risk factors, to accurately predict clinical outcomes and identify targets for prevention and treatment (Silbersweig & Loscalzo, 2017), though this is a long way from clinical practice currently. Part of the hindrance lies with the heterogeneity within current diagnoses and high levels of comorbidities. Due to this, a more multidimensional approach may be required for biomarker development (e.g., as proposed by (Dunlop, 2015; Silbersweig & Loscalzo, 2017). Future research should aim to combine various paths of research, for example, functional brain imaging with endocrinological, genomic, neuropsychological, and behavioural measures alongside clinical features. This integrated approach may be able to provide enhanced markers compared to isolated factors, and enable better stratification and subtyping of disorders, a mechanistic understanding of treatment response and improved tailoring of therapies.

7.4.2 Threat-avoidance in depression and anxiety

We did not provide support for the JORT measuring pathologically relevant concepts in MDD and therefore do not recommend further exploration with this measure in depressed individuals. We suggest that piloting of the task should be conducted in patients with anxiety disorders such as GAD or panic disorder, where stronger associations have been found between threat-avoidance behaviours (Naragon-Gainey, 2010). Improvement (that were suggested in Chapter 6) should first be made to the task to hopefully improve the reliability, validity and robustness of the measure. Tasks measuring deficits in reward

processing via passive avoidance tasks may be more relevant in major depression (Ferster, 1973; Ottenbreit & Dobson, 2004).

7.4.3 Future exploration of the Fake IQ task

Backing up previous findings piloting this measure with patients with anorexia nervosa (Corfield, 2014; Patrick et al., Under Submission), we were able to show that patients with depression and comorbid anxiety showed elevated negative perceived versus actual success on the FIQT compared to controls adding to evidence of concurrent validity of the task. Our neural main effects comparing self-reflection versus control conditions in brain regions relevant to self-reflection and relatedly error processing give us certainty that this measure is tapping psychologically relevant constructs. However, we propose that future use of the FIQT should initially explore the relationship of FIQT performance with alternate measures of self-reflection including self-blame, self-punitiveness, and perfectionism, which seem likely to have associations with FIQT rating. We propose that the measure should be tested within and between different disorders, in particular patients with depression or anxiety (i.e. a non-comorbid patient sample unlike ours – to give certainty that the results are found in specific disorders and not due to comorbidity) and also disorders associated with reduced self-reflections, for example, autism spectrum disorders or schizophrenia (Philippi & Koenigs, 2014). Comparison between different patient groups may highlight distinctions between disorders.

The lack of association between task subscales and treatment response may mean the task measures trait aspects of self-reflection that are unamenable to change. Indeed, low confidence in one's abilities has been found to be a relatively stable trait in individuals generalising across tasks (Ais et al., 2016; Rahnev et al., 2015; Stankov & Crawford, 1997), and having an inherited component (Cesarini et al., 2010) suggesting self-

perception may be a trait level predictor of vulnerability to psychopathology. Our findings of no significant changes in scores over time may therefore show evidence that the task is reliable in measuring this trait disposition. However, further exploration is warranted to substantiate this, especially due to our small sample size. It may be that therapies specifically targeted towards reducing negative self-reflection could lead to more positive reflection on FIQT performance post-therapy. This could be supplemented by testing the measure in at risk and remitted populations to explore if findings in these populations display no significant differences with patient groups, as would be expected if it is a purely trait measure. Similarly testing the measure in healthy controls with knowledge that they perform poorly at cognitive, IQ based tasks and patients who know they perform well could determine the measure's reliability.

Recommendations were made for refinements to the task design in Chapter 4, especially in relation to suitability as a neuroimaging paradigm. We would urge future researchers using this task during scanning to develop an alternative control condition which minimises the possibility for self-reflection; for example, a distractor condition, and refine the timing of reflection conditions. Future work should study the fMRI task in a variety of psychiatric disorders associated with aberrant self-reflection, using larger sample sizes and alternative measures of self-reflection. For example, there is evidence that self-critical behaviours have a separate and independent contribution to anorexia nervosa, beyond that of related depressive symptoms (Dunkley & Grilo, 2007; Starrs et al., 2015), and therefore neural group differences may be displayed in this patient group.

7.4.4 Dynamic functional connectivity in psychopathology

Our work adds to a growing body of evidence that dynamic functional connectivity is altered in various psychopathologies. However, a key barrier to bring this research into

clinical practice is a lack of understanding surrounding what the time-varying property of connectivity means. Future studies should try to clarify the causes of variability and its relationship to static connectivity. Our approach of correlating variability with global self-report measures suggests further exploration of variability and psychological constructs is warranted. Post-scan questioning about the level and quality of self-reflective cognitions engaged in during scanning could help determine links between psychological state and cognitions with connectivity variability, as utilised by Kucyi & Davis (2014) who found a positive correlation between daydreaming during scanning and variability.

The patients included in our work were currently depressed; however, it cannot be concluded that this variability is specific to the depressive state. Future work should investigate dynamic functional connectivity in alternate groups, for example, remitted and at risk populations and those with other disorders relating to aberrant self-reflection to determine whether altered dynamic functional connectivity in the DMN is a vulnerability marker of depression or specific to the depressed state. The findings by Komulainen et al. (2017), which showed that a single dose of mirtazapine altered variability in emotional processing regions, suggest that altered connectivity is a state, rather than trait marker, amenable to change.

7.5 Overall conclusions

The main aim of this work was to examine novel tasks and new analysis techniques to measure threat-avoidance and self-reflection in patients with depression and varying levels of comorbid anxiety. The results suggest further exploration of the Fake IQ test, an implicit measure designed to explore differences between perceived versus actual success, is warranted due to our observed pathological sensitivity and the measure invoking

activation of brain regions involved in error processing and self-reflection. Additionally, we found dynamic functional connectivity abnormalities in regions of the default mode network thought to be crucially involved in the generation of self-reflective cognitions in patients with depression versus controls. We replicated this finding in a second sample of patients with depression, free from comorbidities, suggesting the finding is robust. This is a relatively understudied technique and therefore our work adds to a small body of growing evidence suggesting that psychiatric conditions are associated with aberrant temporal fluctuations in disorder-relevant networks. Meta-analyses showed evidence of consistent neural correlates of psychological therapies across depression and anxiety disorders; however, robust neural predictors of treatment response were not found in the current evidence base. We conclude that the novel task utilised in this thesis to measure pathological threat-avoidance and anticipation is not related to depression, but deserves exploration in pure anxiety disorders due to previous findings that anxiolytic medication altered behaviour on the task (Perkins et al., 2013, 2009). The clinical implications of the findings have been described in relation to the importance of negative self-reflective cognitions in affective disorders and future recommendations made regarding improvements to neuroimaging studies of treatment response and how this could enhance the speed of robust biomarker development for use in clinical practice.

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Appendices

Appendix 1: Search terms for meta-analyses

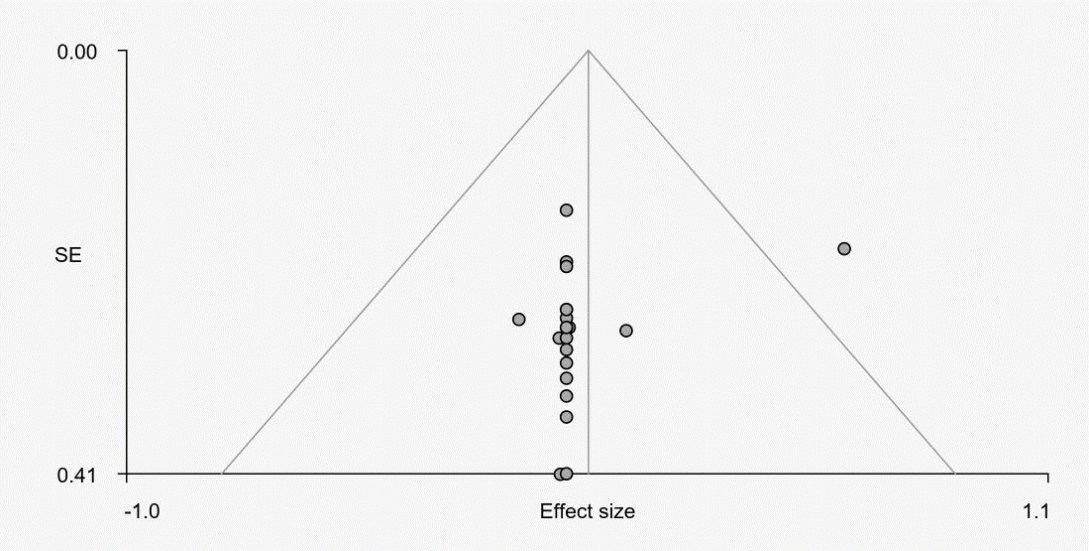
The title, abstract and keywords of Scopus (Elsevier, Amsterdam, Netherlands, http://www.scopus.com) and Medline (Ovid Technologies, Inc., http://ovidsp.uk.ovid.com were searched for the following words:

(("psychotherapy" OR ("psychological" AND "therapy") OR "CBT" OR ("cognitive" AND "therapy") OR ("behavio*" AND "therapy") OR ("interpersonal" AND "therapy") OR "psychoeducation*" OR ("exposure" AND "therapy") OR "psychodynamic" OR "mindful*") AND ("*MRI" OR "SPECT" OR "magnetic resonance imaging" OR "tomography" OR "PET" OR "positron emission") AND ("anxi*" OR "depress*" OR "anxious" OR "traumatic" OR ("obsess" AND "compul*") OR "phobia" OR "panic" OR "bipolar" OR "manic" OR "dysthymi*" OR "melancholi*" OR "cyclothymi*" OR "seasonal affect*"))

Appendix 2: Funnel plots from meta-analyses

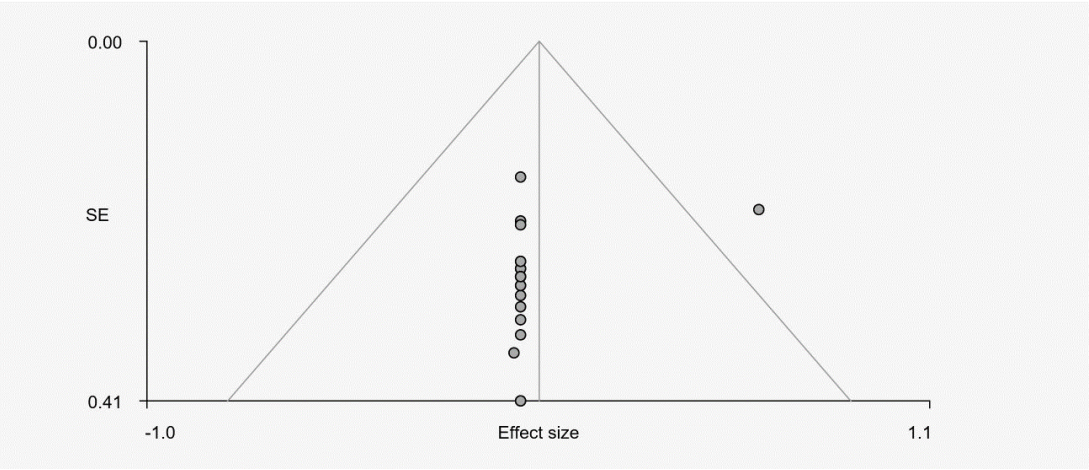
Funnel plots from regions of significant difference in brain activation change pre-to post-treatment (both task and resting state studies included):

1) Right inferior network, inferior longitudinal fasciculus



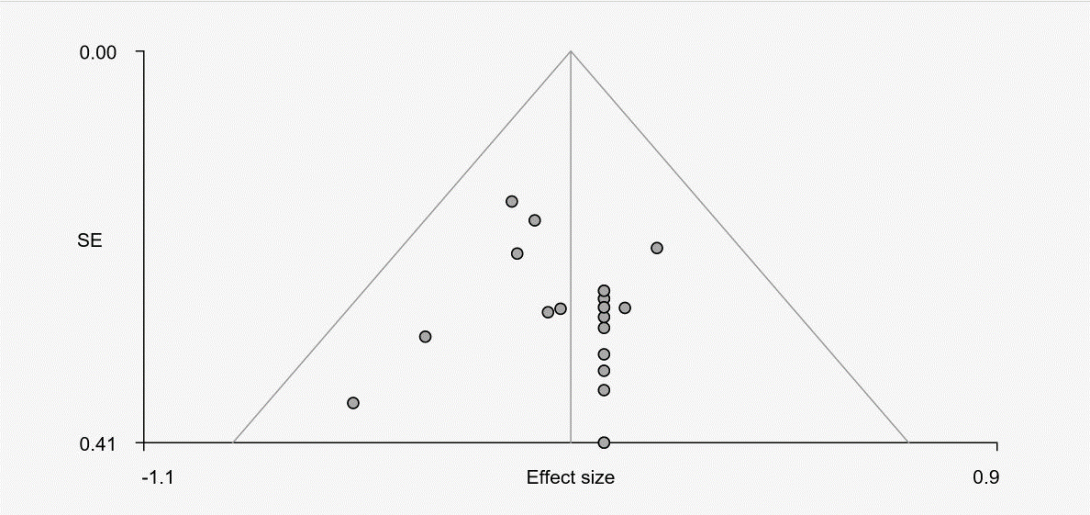
Egger test: Bias = -0.83, t = 1.38, df = 21, p = 0.182

2) Right arcuate network, posterior segment



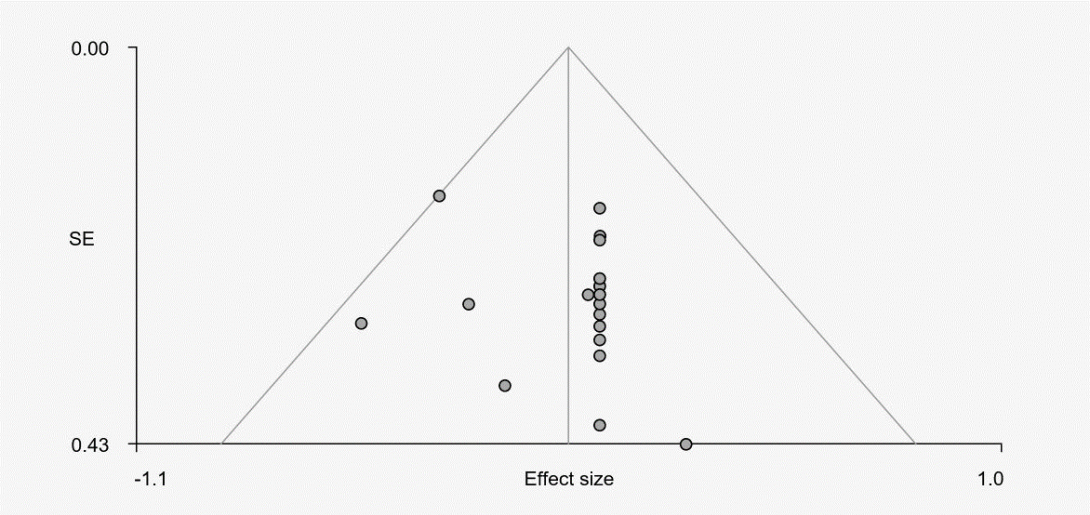
Egger test: Bias = -0.86, t = -1.44, df = 21, p = 0.164

3) Left anterior cingulate/paracingulate gyri



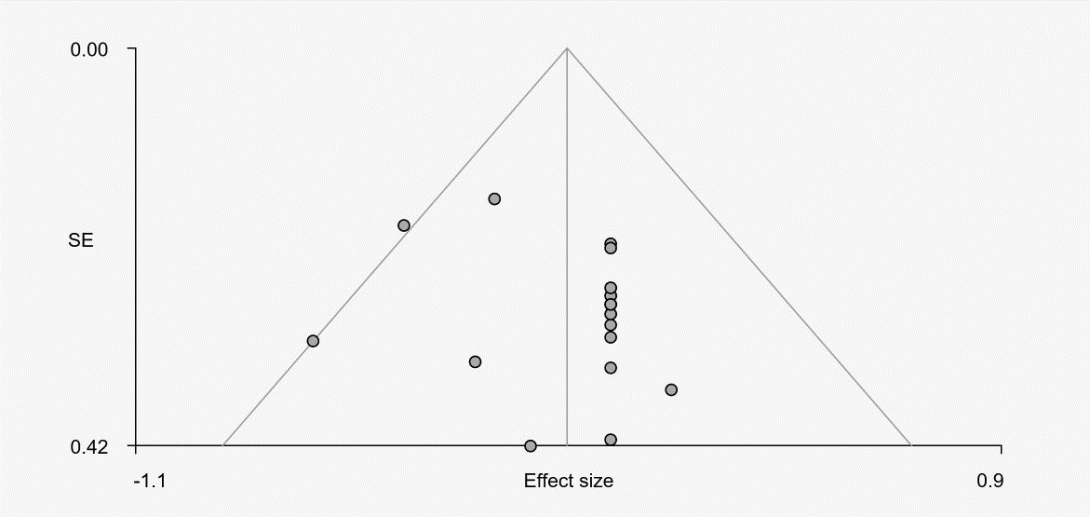
Egger test: Bias = 0.36, t = 0.72, df = 21, p = 0.479

4) Left inferior frontal gyrus, opercular part, left insula



Egger test: Bias = 0.73, t = 1.26, df = 21, p: 0.220

5) Right inferior frontal gyrus, triangular part

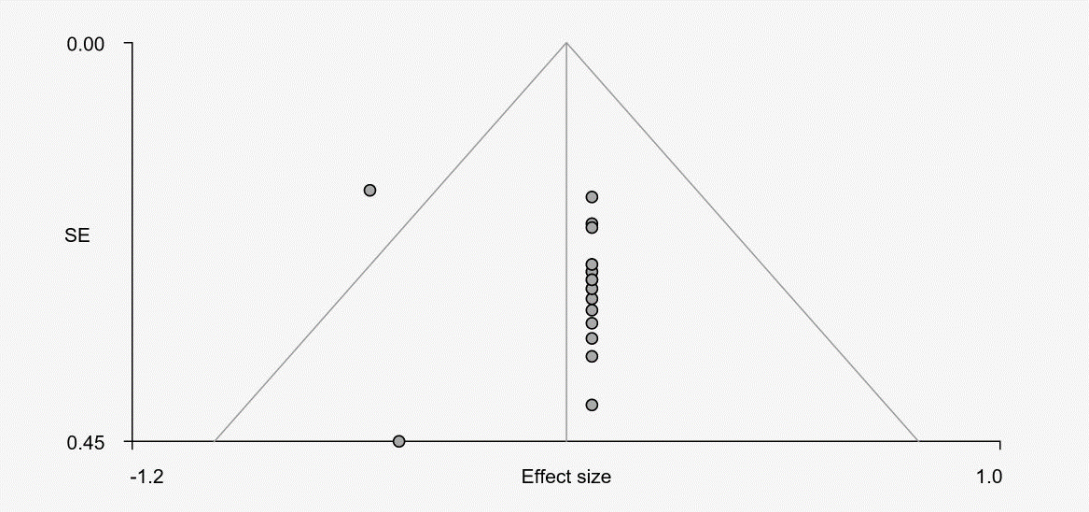


Egger test: Bias = 1.06, t = 1.57, df = 21, p = 0.131

6) Left middle frontal gyrus

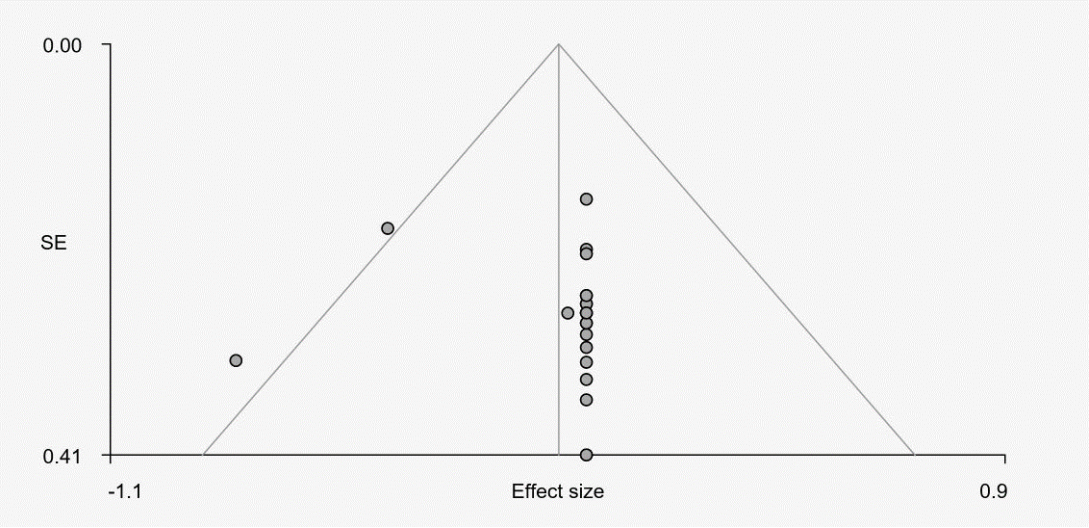
Egger test: Bias = 0.70, t = 0.93, df = 21, p = 0.365

7) Right temporal pole, middle temporal gyrus



Egger test: Bias = 1.03, t = 1.64, df = 21, p = 0.115

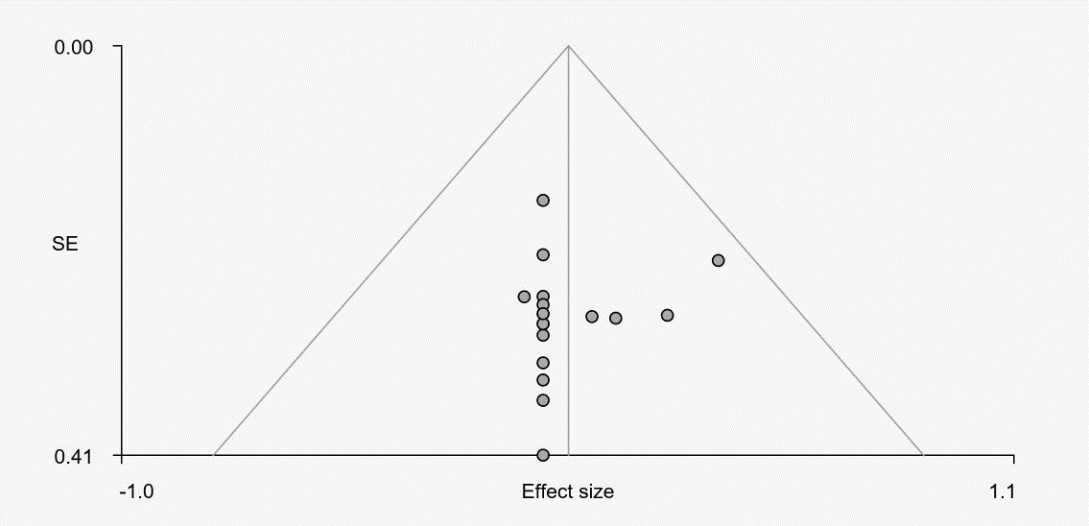
8) Right middle frontal gyrus, orbital part



Egger test: Bias = 0.29, t = 0.45, df = 21, p = 0.656

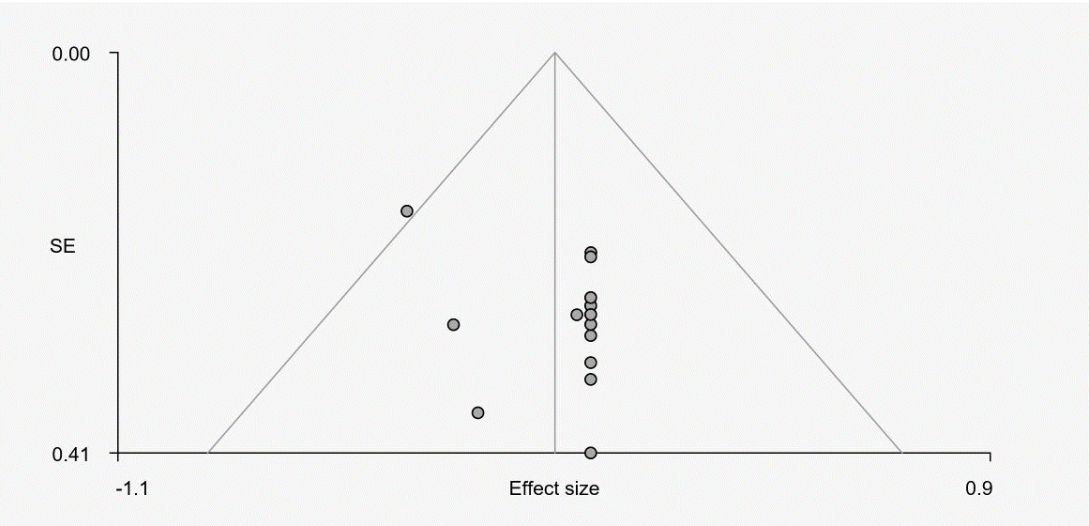
Funnel plots from regions of significant difference in brain activation change pre-to post-treatment– task-based studies only

1) **Right and left precuneus/corpus callosum**



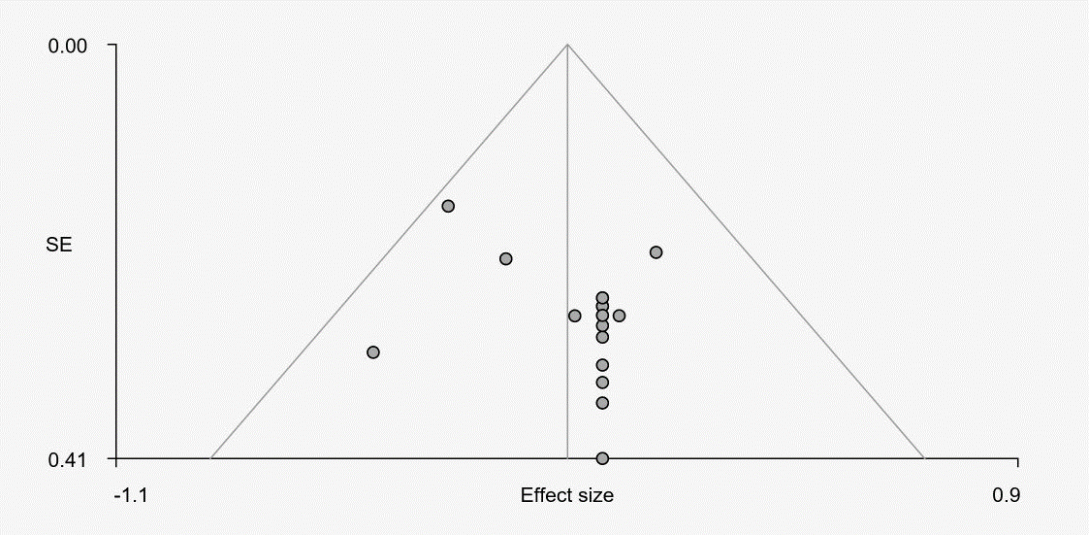
Egger test: Bias = -0.19, t = -0.34, df = 16, p = 0.739

2) **Left inferior frontal gyrus, opercular part**



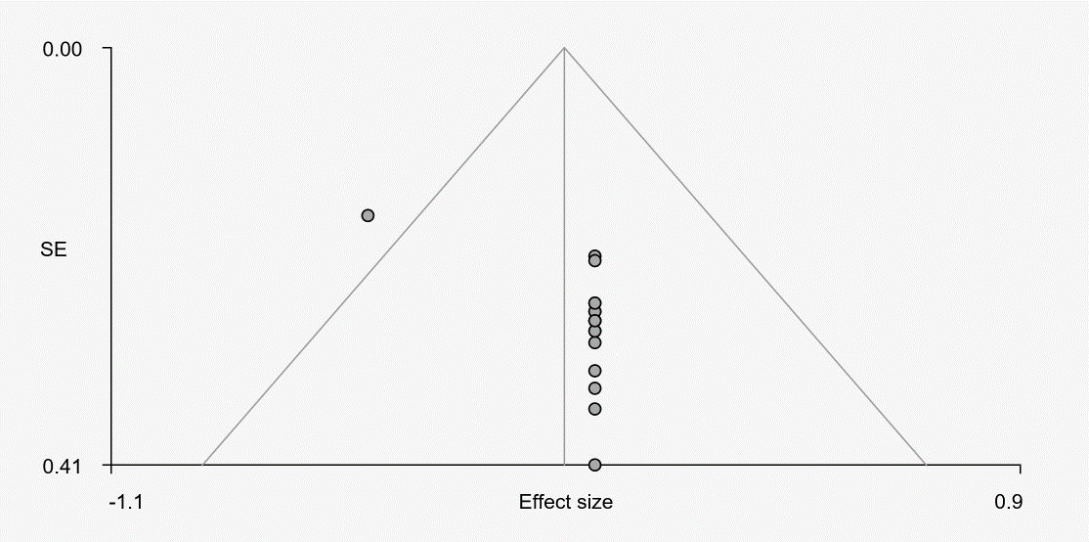
Egger test: Bias = 1.37, t = 2.14, df = 16, p = 0.048

3) Left anterior cingulate / paracingulate gyri / right anterior cingulate



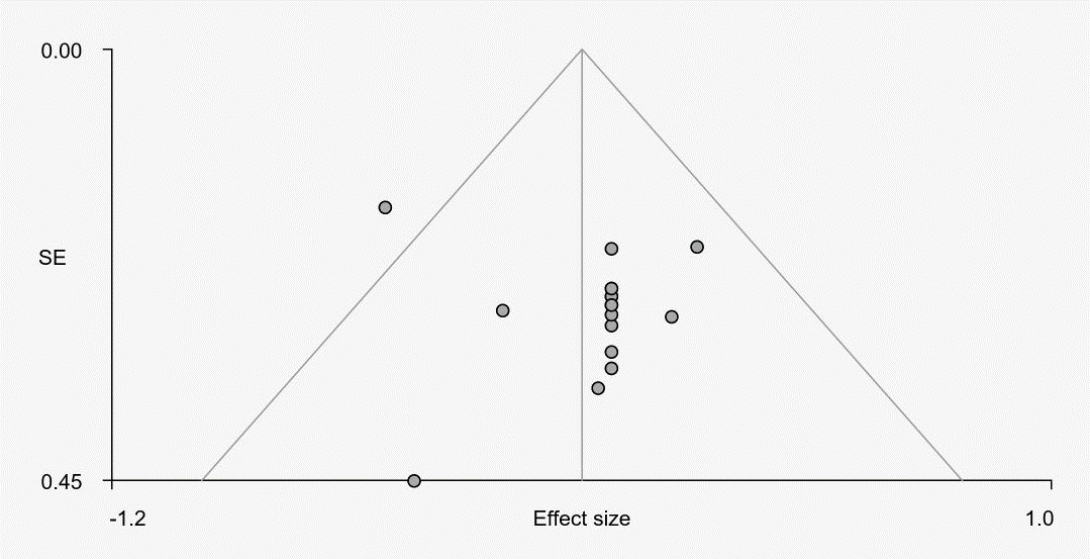
Egger test: Bias = 1.22, t = 1.80, df = 16, p = 0.091

4) Left insula



Egger test: Bias = 2.13, t = 3.44, df = 16, p: 0.003

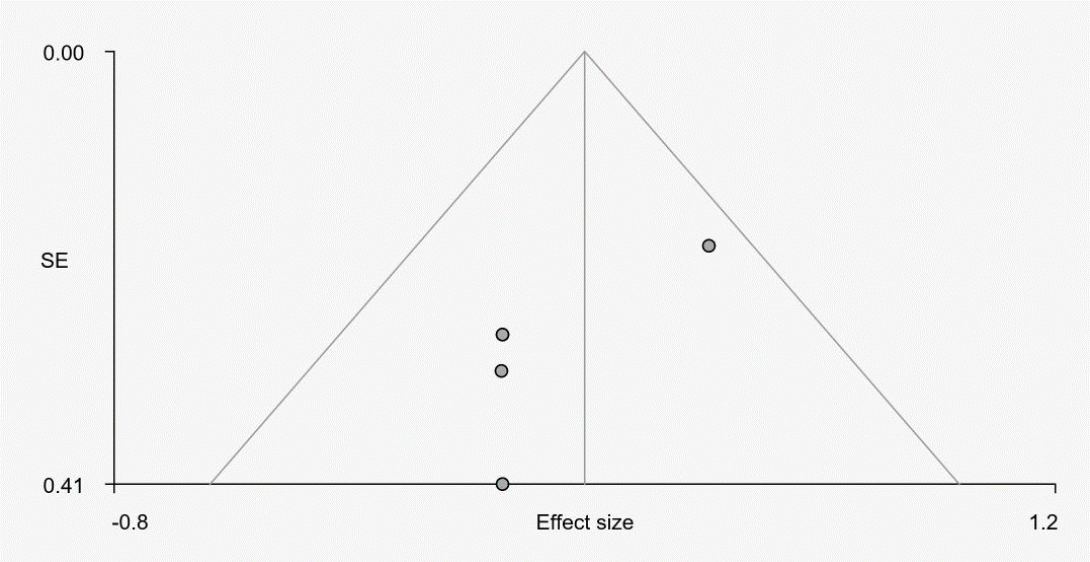
5) **Right temporal pole, middle temporal gyrus**



Egger test: Bias = 1.21, t = 1.32, df = 16, p = 0.206

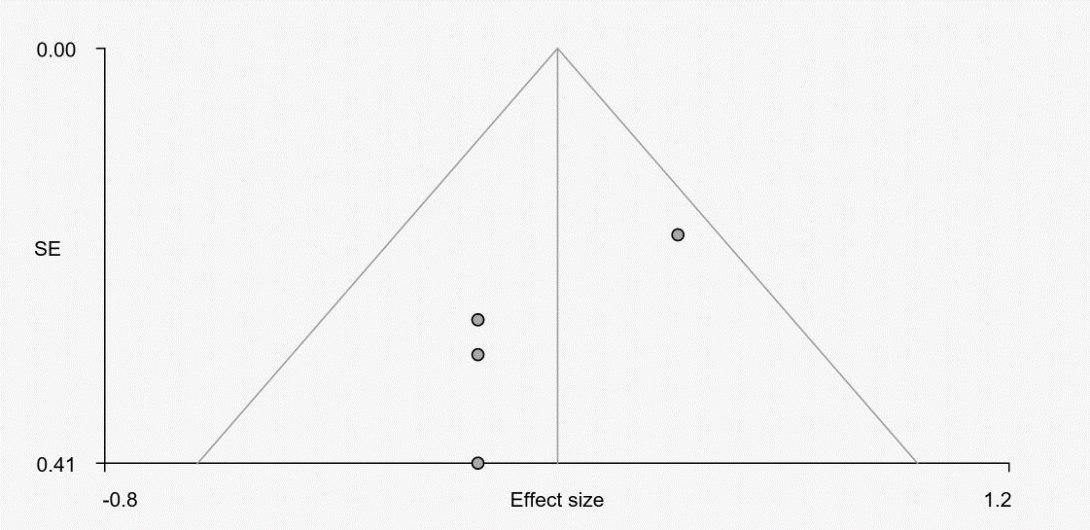
Funnel plots from regions of significant difference in brain activation change pre-to post-treatment – resting-state studies only

1) **Right lingual gyrus / right inferior network, right fusiform gyrus**



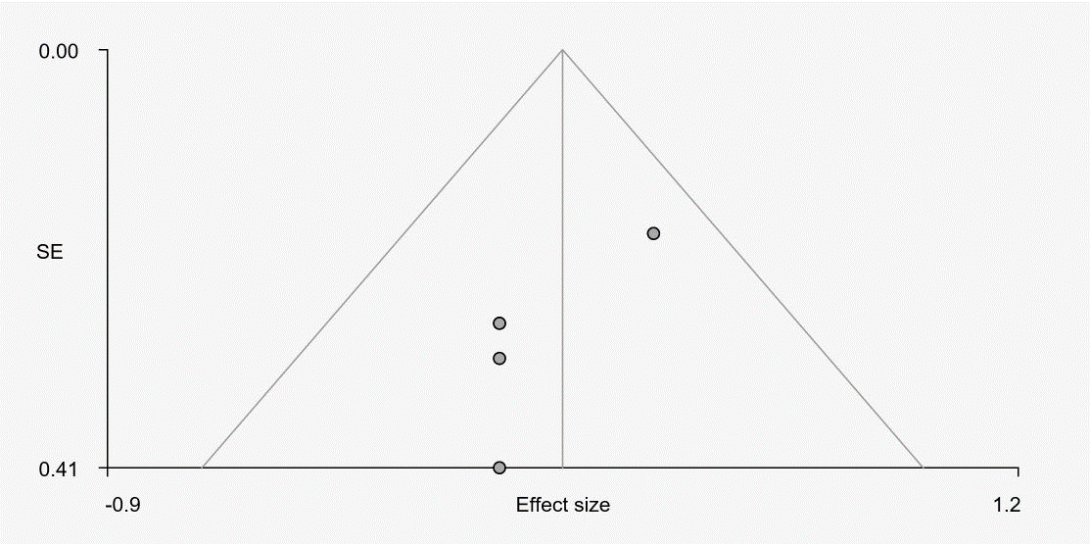
Egger test: Bias = -2.75, t = -2.59, df = 3, p = 0.081

2) Right arcuate network, posterior segment



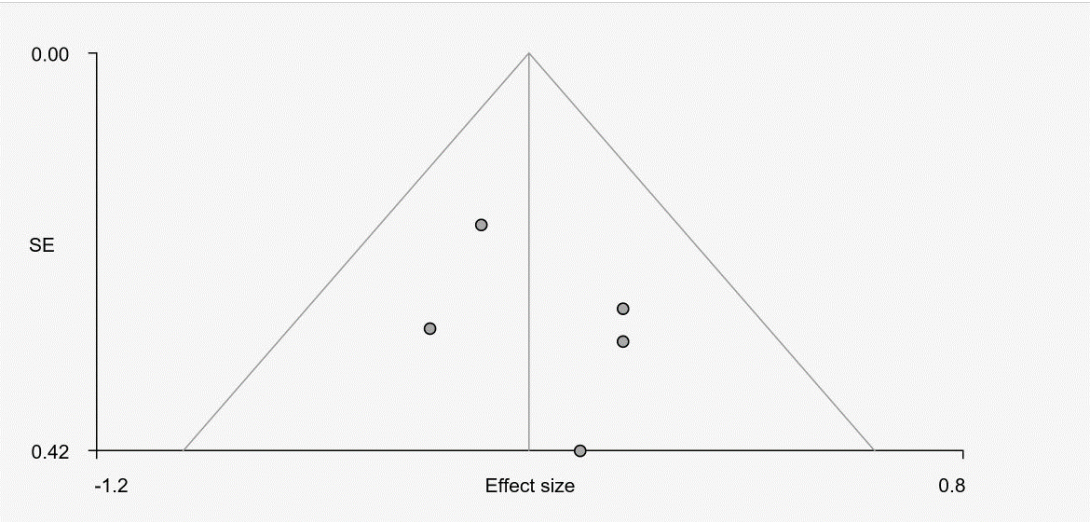
Egger test: Bias = -2.77, t = -2.58, df = 3, p = 0.082

3) Corpus callosum



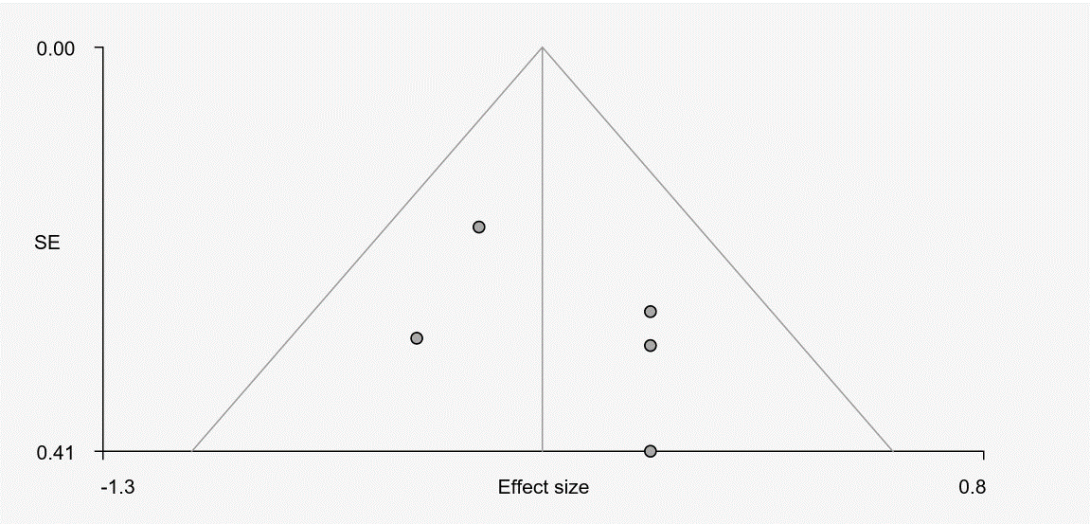
Egger test: Bias = -2.11, t = -2.71, df = 3, p = 0.073

4) Right middle frontal gyrus, right inferior frontal gyrus



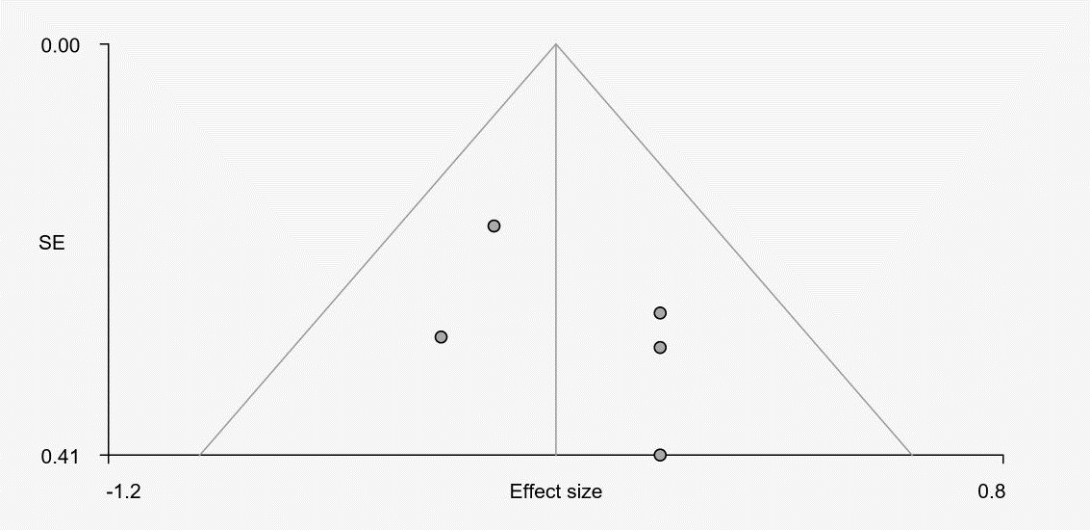
Egger test: Bias = 1.19, t = 0.92, df = 3, p = 0.427

5) Left middle frontal gyrus



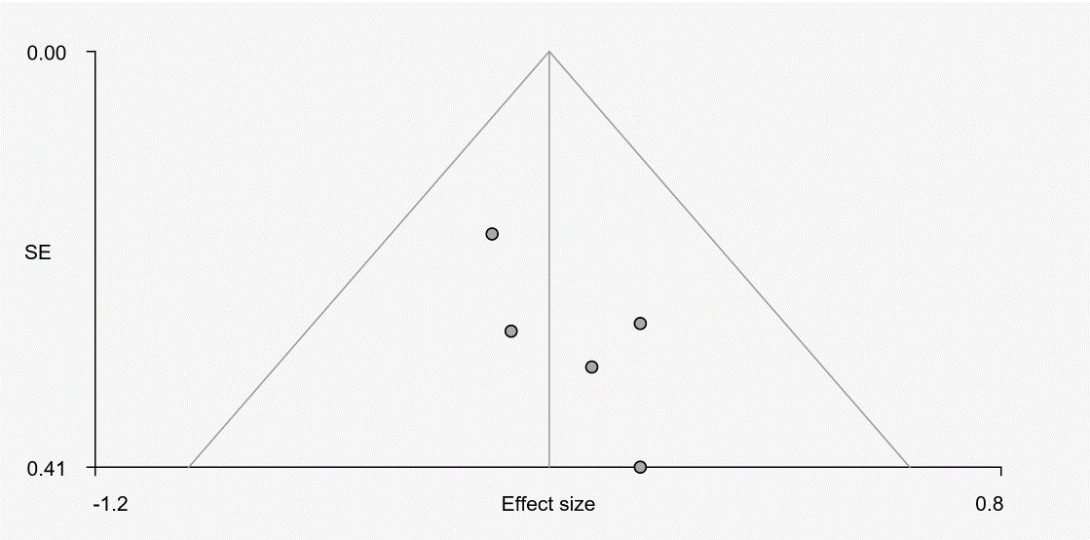
Egger test: Bias = 1.69, t = 1.10, df = 3, p = 0.354

6) Right middle frontal gyrus, orbital part



Egger test: Bias = 1.66, t = 1.17, df = 3, p = 0.326

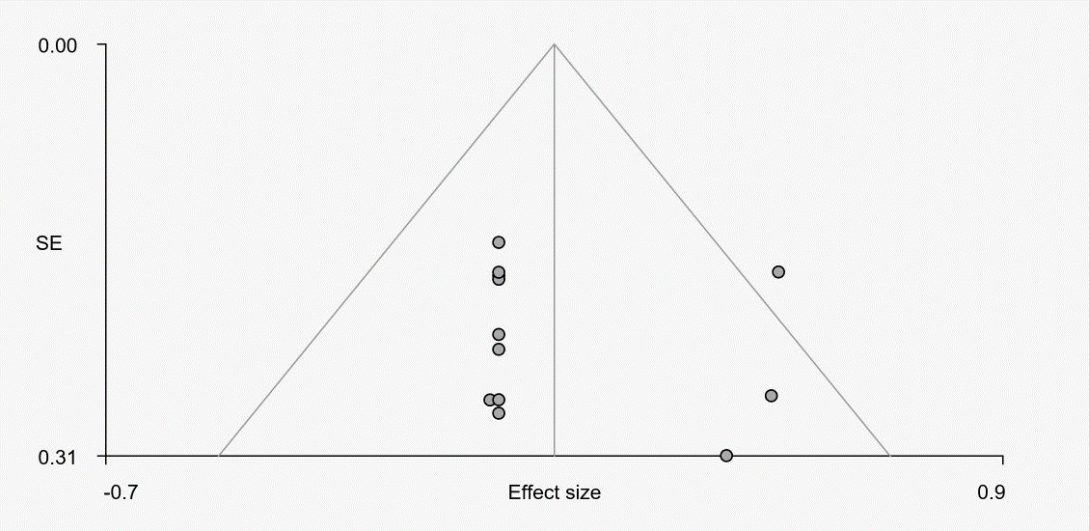
7) Right anterior cingulate / paracingulate gyri / left anterior cingulate



Egger test: Bias = 1.55, t = 1.98, df = 3, p = 0.142

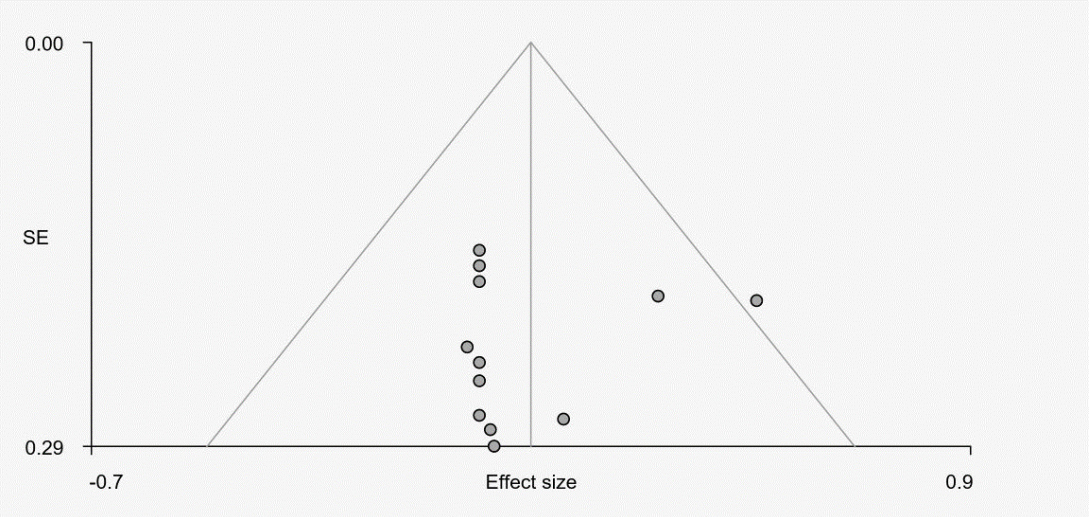
Funnel plots for regions significantly predicting symptomatic improvement

1) Right cuneus cortex



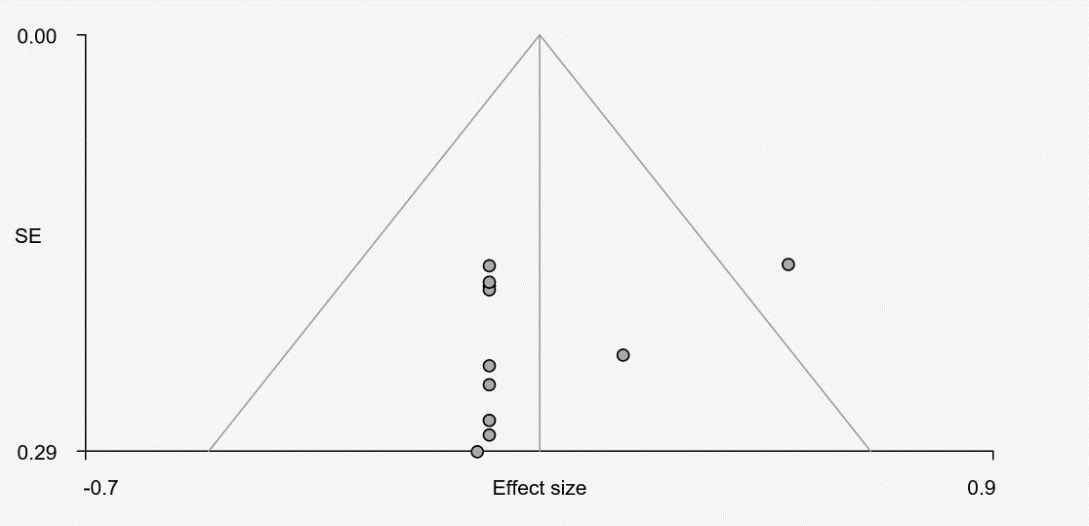
Egger test: Bias = 0.65, t = 0.50, df = 10, p = 0.631

2) Left medial cingulate / paracingulate gyri / left anterior cingulate



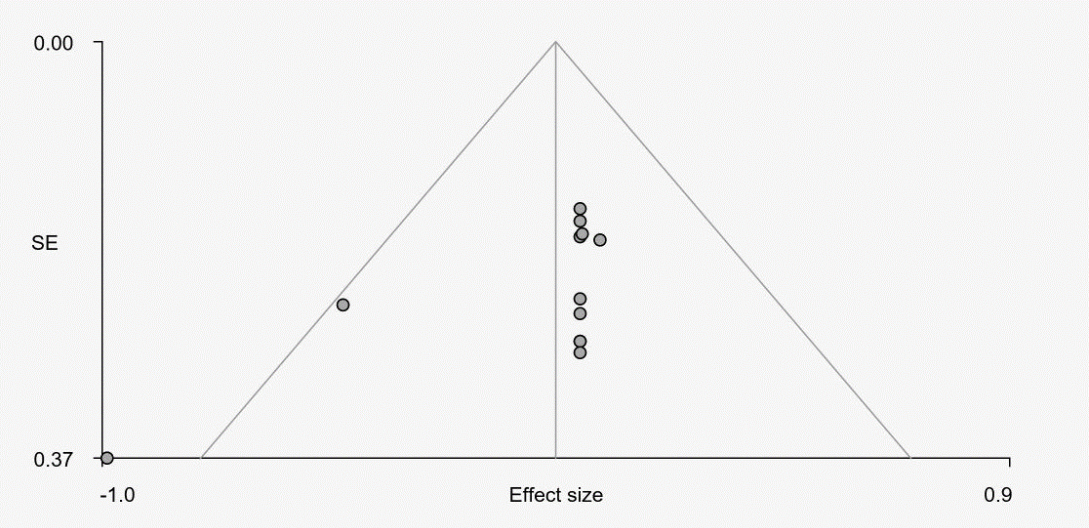
Egger test: Bias = -0.32, t = -0.28, df = 10, p = 0.785

3) Right frontal orbitopolar tract



Egger test: Bias = -1.34, t = -1.09, df = 10, p = 0.300

4) Left precentral / postcentral gyrus



Egger test: Bias = -2.14, t = -2.17, df = 10, p = 0.055

Appendix 3: Standardised participant instructions for the Fake IQ test

In this experiment, we will test your visual perception ability. This is a property of your brain which is thought to be linked to intelligence. In order to accomplish this, we will ask you briefly to look at some images and make quick, accurate assessments of their properties.

You will be shown two images side by side and asked to select one of them according to a previously specified criterion, for example, which shape has the largest surface area or volume or contains the most elements. Some of the differences between the images may be very subtle and difficult to perceive but please do your best to make a judgement. You select an image by pressing either the left- or right-hand key of your button box.

After each image, you will be asked either to think about how satisfied you were with your performance or to relax and wait for the next trial. When presented with the word "SATISFIED" please think carefully about how satisfied you were with your performance on that last trial. This is an important test of your analytical ability. If you are presented with the word "WAIT" please wait for the next trial, relax and clear your mind. Try not to think about your performance on the previous trials.

In between trials you will see a cross. Look at the cross and wait for the next two images to appear on the screen.

After every 10 trials you will be asked 3 questions about your performance on the previous 10 images presented. This part of the experiment is an important test of your analytical ability so please think carefully about your ratings of your performance. Please click on the appropriate answer on a scale by pressing down on either the left or right-hand side of the button box to move the pointer on the response box.